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Venous Thromboembolism Prophylaxis in Major Orthopedic Surgery: Systematic Review Update

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may periodically be assessed for the currency of conclusions. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program Web site at www.effectivehealthcare.ahrq.gov. Search on the title of the report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

If you have comments on this systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Technical Expert Panel

In conducting a surveillance of the literature since the prior AHRQ report on venous thromboembolism prophylaxis in orthopedic surgery, we consulted several technical, content, and clinical experts. The Technical Experts provided comment on their interpretation of the current state of the evidence and of clinical questions that are currently pertinent to patient management and decisionmaking. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

The list of Technical Experts who provided input to this report [will be included in the final report]:

Venous Thromboembolism Prophylaxis in Major Orthopedic Surgery: Systematic Review Update

Structured Abstract

Background. Major orthopedic surgery carries a high risk for venous thromboembolism (VTE)—deep vein thrombosis (DVT) and pulmonary embolism (PE). The major orthopedic surgeries of greatest concern include total knee replacement (TKR), total hip replacement (THR), and hip fracture (HFx) surgeries. A variety of strategies to prevent VTE are available, including pharmacological (antiplatelet, anticoagulant) and mechanical modalities. The 2012 Comparative Effectiveness Review on Venous Thromboembolism Prophylaxis in Orthopedic Surgery addressed many of the uncertainties in this area. Through a literature surveillance process, it was determined that the 2012 review requires updating.

Methods. Three Key Questions (KQ) from the 2012 review have been revised and updated, and three new KQs have been added. All KQs pertain to patients undergoing major orthopedic surgeries (TKR, THR, and HFx surgery). All KQs address comparative effectiveness regarding postoperative rates of VTE (DVT and PE), major bleeding, other adverse events, and adherence. The KQs address comparisons of different classes of thromboprophylaxis interventions (KQ 1); individual interventions within classes (KQ 2); different doses, regimens, and treatment durations (KQ 3); combined versus single classes (KQ 4); network meta-analyses comparing classes and individual interventions on total DVT and major bleeding (KQ 5); and starting pharmacologic thromboprophylaxis at different times relative to surgery (KQ 6). Comprehensive literature searches were conducted in PubMed®, both the Cochrane Central Trials Registry® and Cochrane Database of Systematic Reviews®, and EMBASE® databases from 2010 through December 23, 2015 [to be updated]. Eligible studies from the 2012 report, other existing systematic reviews, recent conference proceedings, and ClinicalTrials.gov were included. All randomized controlled trials (RCT) and nonrandomized comparative studies (NRCS) with at least 750 participants (and at least 50 participants per study arm) were included. Abstracts and potentially relevant full-text articles were double screened. Eligible studies were extracted into tested data extraction forms. Study risk of bias was assessed. Pairwise, random effects model meta-analyses were conducted when at least four studies evaluated a given comparison. Random effects model Bayesian network meta-analyses were conducted to address KQ 5. Strength of evidence for each KQ was evaluated.

Results: There were 120 RCTs and 14 NRCSs that met eligibility criteria comparing interventions for the three surgeries. For patients undergoing THR, there is moderate to high SoE that direct factor Xa inhibitors (FXaI) and direct thrombin inhibitors (DTI) are each more effective than either low molecular weight heparin (LMWH) or mechanical devices (dynamic, intermittent or static devices that aim to minimixe stasis) to prevent VTE. These are in turn more effective than either unfractionated heparin (UFH) or vitamin K antagonists (VKA). FXaI and UFH result in more major bleeding episodes than DTI or LMWH; LMWH results in more major bleeding than VKA. For patients undergoing TKR, there is low to moderate SoE that FXaI is similar in effect or more effective in preventing VTE than LMWH. LMWH and VKA are similarly effective in preventing VTE. All have similar risks for major bleeding. For patients undergoing HFx surgery, there is insufficient evidence regarding relative effectiveness or

adverse event risk of interventions. Regarding other Key Questions (beyond comparative effectiveness of intervention classes), there is sufficient evidence to conclude that for patients undergoing THR, dalteparin (a LMWH) is most effective to prevent total DVTs, followed by enoxaparin (a LMWH), (unfractionated) heparin, and, finally, warfarin (a VKA). There is also sufficient evidence to conclude that lower dose and/or longer duration LMWH is more effective to prevent total VTE (than higher dose or shorter duration LMWH). There is no evidence of significant differences between different LMWH doses to prevent proximal DVTs or avoid major bleeding. There is also no evidence of significant differences in total VTE between different doses of either the same or different FXaI. For all other interventions, comparisons, outcomes, and KQs there is insufficient evidence.

Conclusions: While a large body of RCT evidence exists on comparative effectiveness and harms of venothromboprophylaxis interventions after major orthopedic surgery, none of the KQs are fully and adequately addressed. The largest body of evidence exists for THR, with fewer studies of TKR, and very few studies of HFx surgery. The large majority of studies evaluated LMWH (and enoxaparin, in particular) with relatively few studies evaluating other intervention classes. Future studies, particularly of interventions other than enoxaparin, are needed to address most Key Questions. All studies should report all VTE-related and adverse event outcomes. Larger trials should conduct and report subgroup analyses of interest.

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Executive Summary

Introduction

Major orthopedic surgery carries a high risk for venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE).[1] The major orthopedic surgeries of greatest concern include total knee replacement (TKR), total hip replacement (THR), and hip fracture (HFx) surgeries. PE, an obstruction of a pulmonary artery or its branches usually by an embolic thrombus, is potentially life-threatening and can result in chronic complications with generally poor prognosis, such as thromboembolic pulmonary hypertension.[2-4] DVTs are the principal intermediate process necessary for surgery-related PE and increase the risk of PE.[5] In addition, about 5 to 10 percent of patients with symptomatic DVTs develop severe postthrombotic syndrome, which may include venous ulcers, intractable edema, and chronic pain; although, these outcomes may take 10 years or more to develop.[6] Estimates suggest that in current practice about 4.7 percent of patients undergoing major orthopedic surgery would have symptomatic VTE without prophylaxis.[1]

A variety of strategies to prevent VTE are available, including pharmacological (antiplatelet, anticoagulant) and mechanical modalities.[1] Pharmacologic prophylactic treatments include unfractionated heparin (UFH), low molecular weight heparin (LMWH), vitamin K antagonists (VKA), antithrombin III-mediated selective factor Xa inhibitors (ATIII), direct factor Xa inhibitors (FXaI), bivalent and univalent direct thrombin inhibitors (DTI), and antiplatelet agents. Mechanical prophylaxis aims to minimize stasis, the principal putative factor resulting in venous thrombosis. It can be dynamic and intermittent (e.g., intermittent pneumatic compression device [IPC]) or static (e.g., graduated compression stockings [GCS]). The modalities can be used alone or in combination, at variable doses (of drugs) or regimens (of mechanical devices; e.g., different pressure or compression frequency), and for different durations. However, prophylaxis with pharmacologic strategies also has important potential harms (risks) including major bleeding, prosthetic joint infections, and the need for reoperation, which may all lead to death or permanent removal of the prosthetic joint. Mechanical modalities (when used alone), however, are thought to be inferior to pharmacological agents to prevent VTE.

VTE prophylaxis (or "thromboprophylaxis") is now standard of care for patients undergoing major orthopedic surgery. Prophylaxis has been demonstrated to reduce the incidence of symptomatic and asymptomatic DVT (in comparison to placebo or no prophylaxis); however, because of rarity of postoperative PE,[1] the body of randomized controlled trial (RCT) evidence is not adequately powered to demonstrate the effect of prophylaxis on PE. The effect of prophylaxis on DVT risk reduction is generally considered an adequate proxy for likely PE risk reduction, but it remains unknown to what extent reducing the incidence of DVTs impacts the magnitude of any reduction in the incidence of PEs. Avoiding DVT is a clinically worthwhile goal to reduce the incidence of lower extremity venous disease,[7] such as postphlebitic syndrome,

venous insufficiency,[8, 9] and phlegmasia cerulean dolens (resulting in edema, pain, and gangrene).[10]

Scope and Key Questions

Scope

The 2012 Comparative Effectiveness Review on Venous Thromboembolism Prophylaxis in Orthopedic Surgery[11] (hereafter "the 2012 VTE report") addressed many of the uncertainties in this area, including questions regarding the natural history of VTE, predictors of VTE, and the likelihood that DVTs result in PE in patients undergoing THR, TKR, or HFx surgery; the comparative efficacy of VTE prophylaxis strategies with no VTE prophylaxis, within and between classes of VTE prophylaxis modalities, and duration of VTE prophylaxis in patients undergoing these surgeries; and the efficacy of VTE prophylaxis in nonmajor orthopedic surgeries (knee arthroscopy, surgical repair of lower extremity injuries distal to the hip, and elective spine surgery). The 2012 VTE report included studies published from 1980 through May 2011. It found a general dearth of evidence regarding important clinical outcomes (nonfatal PE, fatal PE, major bleeding, reoperation), but high strength of evidence that pharmacologic VTE prophylaxis reduces the risk of DVT compared to no VTE prophylaxis and increases the risk of minor bleeding. Comparisons of mechanical VTE prophylaxis versus no VTE prophylaxis did not provide strong evidence that mechanical prophylaxis reduced the risk of VTE, including, specifically, DVT. The comparisons of different classes of VTE prophylaxis modalities (e.g., different pharmacologic classes or pharmacologic versus mechanical VTE prophylaxis) provided neither adequate evidence for important clinical outcomes nor strong evidence for other outcomes, including DVT. There were few studies evaluating the new FXaIs. In general, different interventions within classes were not statistically significantly different in their effects on DVT or bleeding. There was not strong evidence for other Key Questions.

We conducted a surveillance review of new studies potentially eligible to update all Key Questions from the 2012 VTE report. The surveillance review is summarized in the online protocol for this review.[12] Upon discussion of the current state of the evidence with a panel of technical experts, we determined that a focused update of the 2012 AHRQ report would be of greatest value. Based on their input and the findings of the surveillance review, we focused the update on comparisons between specific prophylaxis interventions; different classes of intervention; different doses, regimens, and treatment durations of interventions; different combinations of interventions; and different timing of starting prophylaxis (in relation to the time of surgery).

The objectives for the systematic review are to update the 2012 VTE report focused on the comparative effectiveness (for VTE outcomes and harms) of different thromboprophylaxis interventions for patients undergoing major orthopedic surgery (THR, TKR, and HFx surgery).

Key Questions

The following are the Key Questions (KQ) addressed by the review:

KQ 1 (update of original KQ 5): In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy between classes of thromboprophylaxis interventions on venous thromboembolism outcomes, treatment adherence, major bleeding, and other adverse events?

KQ 2 (update of original KQ 6): In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy of individual thromboprophylaxis interventions within classes (low molecular weight heparin, factor Xa inhibitors, direct thrombin inhibitors, and mechanical devices) on venous thromboembolism outcomes, treatment adherence, major bleeding, and other adverse events?

KQ 3 (new KQ based on original KQ 8): In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy of different doses, regimens, or treatment durations of the same thromboprophylaxis interventions (low molecular weight heparin, factor Xa inhibitors, direct thrombin inhibitors, and mechanical devices) on venous thromboembolism outcomes, treatment adherence, major bleeding, and other adverse events?

KQ 4 (update of original KQ 7 plus expansion): In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy of combined classes of thromboprophylaxis interventions versus single classes on venous thromboembolism outcomes, treatment adherence, major bleeding, and other adverse events?

KQ 5 (new KQ): In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), based on network meta-analysis, what are the comparative effects of thromboprophylaxis interventions on deep vein thrombosis and, separately, major bleeding?

- What are the comparative effects of different classes of thromboprophylaxis interventions?
- What are the comparative effects of different individual thromboprophylaxis interventions?

KQ 6 (new KQ): In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy of starting pharmacologic thromboprophylaxis at different times (i.e., preoperative, intraoperative, postoperative) on venous thromboembolism outcomes, treatment adherence, major bleeding, and other adverse events?

Methods

The Brown Evidence-based Practice Center (EPC) conducted the review based on a systematic review of the published scientific literature, using established methodologies as outlined in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[13]

Search Strategy

A comprehensive search of the scientific literature was conducted to identify relevant studies addressing the KQs that have been published since the 2012 VTE report, which included studies published from 1980 through May 2011. We searched PubMed®, both the Cochrane Central Trials Registry® and Cochrane Database of Systematic Reviews®, and EMBASE® databases. Searches were limited to 2010 through December 23, 2015 [to be updated]. We included an overlap of more than 1 year with the search done for the 2012 VTE report. The updated literature searches replicated the searches from the 2012 VTE report and added additional terms for new treatments (e.g., factor Xa inhibitors [FXaI]). The search strategy was peer reviewed by an independent, experienced information specialist/librarian.

We also searched the ClinicalTrials.gov registry and the Food and Drug Administration, Healthy Canadians, and the U.K. Medicines & Healthcare products Regulatory Agency Web sites for relevant documents from 2011 through July 27, 2015; no additional studies were found. In addition, the reference lists of published clinical practice guidelines, systematic reviews, and Scientific Information Packages from manufacturers were hand-searched, and the Technical Expert Panel (TEP) members were invited to provide references of new studies. Existing systematic reviews were used primarily as sources of new studies. With the exception of studies included in the 2012 VTE report, we extracted and incorporated any studies *de novo* and did not summarize or incorporate the existing systematic reviews. All articles identified through these sources were screened for eligibility using the same criteria as was used for articles identified through literature searches.

All studies cited and tabulated in the 2012 VTE report were screened for eligibility on a par with new studies. However, as noted below, we relied on the summary tables in the 2012 VTE report for data from these studies.

[Peer and public review will provide an additional opportunity for experts in the field and others to ensure that no relevant publications have been missed. The search will be updated in all databases upon submission of the draft report for peer and public review. All summaries and qualitative and quantitative analyses in the update will incorporate all relevant studies, regardless of their source.]

Study Eligibility Criteria

The current eligibility criteria are mostly similar to the criteria used in the 2012 VTE report, as pertain to updated KQs.

Populations of Interest

For all KQs, studies of patients undergoing major orthopedic surgery (THR, TKR, HFx) were eligible. In contrast with the 2012 VTE report, we excluded studies that included more than one type of surgery but did not report results separately by surgery type. We did not exclude studies based on details regarding the type of eligible surgery, related anesthesia management, or perioperative care. Subpopulations of interest included those defined by age, race/ethnicity, health status, comorbidities, prior history of abnormal surgical bleeding or bleeding disorder, prior medications (e.g., antiplatelet drugs), kidney function, and treatment adherence/compliance.

Interventions of Interest

The interventions of interest for all KQs included pharmacological VTE prophylaxis agents within the defined classes of oral antiplatelet agents, injectable low molecular weight heparin (LMWH), injectable unfractionated heparin (UFH), injectable or oral factor Xa inhibitors (FXaI), injectable or oral direct thrombin inhibitors (DTI), and oral vitamin K antagonists (VKA), and mechanical VTE prophylaxis devices within the classes graduated compression stockings (GCS), intermittent pneumatic compression devices (IPC), and venous foot pumps (VFP). We also included studies of prophylactic interior vena cava filters for KQs 1 and 5 (that compared classes of interventions). We included multimodality therapies KQ 3 (different doses, regimens, or treatment durations). We included studies of combination therapies (e.g., drug + mechanical prophylaxis) for KQs 4 and 5 and of different starting times relative to surgery for KQ 6.

Comparators of Interest

We included any of the above interventions as comparators as pertinent, including

- KQ 1 intervention in a different class
- KQ 2 intervention within the same class
- KQ 3 same intervention with different (lower) dose (or anticoagulation goal), (less intensive) regimen, or (shorter) duration
- KQ 4 single modality intervention
- KQ 5 Same as KQ 1 and KQ 2, plus placebo and no thromboprophylaxis study arms
- KQ 6 same intervention started at different (later) time relative to surgery

Outcomes of Interest

For all KQs, except KQ 5 (the network meta-analysis), we evaluated the following outcomes:

- VTE (combined PE and DVT)
    - Total VTE (symptomatic and asymptomatic)
    - Symptomatic VTE
- PE
    - Total PE (fatal and nonfatal; symptomatic and asymptomatic)
    - Fatal PE
    - Symptomatic PE

- DVT
    - Total DVT (symptomatic and asymptomatic; proximal and distal)
    - Symptomatic DVT
    - Proximal DVT
- Postthrombotic syndrome (PTS)
- Pulmonary hypertension (due to PE)
- Adherence (compliance) with treatment
- Adverse events due to intervention(s)
    - Major bleeding, including:
        - Fatal bleeding
        - Bleeding leading to transfusion
        - Major bleeding leading to reoperation
        - Major bleeding leading to readmission
        - Surgical site / joint bleeding
        - Bleeding leading to infection
        - As defined by authors
    - Surgical site/wound-related infections
    - Surgical site/wound complications (other than bleeding, infection)
    - Heparin-induced thrombocytopenia
    - Adverse events due to mechanical devices (as reported by authors)
    - Adverse events due to IVC filter (as reported by authors)
    - Other clinically significant adverse events reported by studies

For KQ 5 (the network meta-analysis), we evaluated only *total DVT* and *major bleeding*. We included confirmed and unconfirmed VTE, but downgraded the risk of bias for those studies that analyzed unconfirmed VTE. If both confirmed and unconfirmed VTE were reported, we extracted only the confirmed VTE data.

Eligible Study Designs

For all KQs, we included randomized controlled trials (RCT) of any sample size. For KQs other than the network meta-analysis (KQ 5), we also included prospective or retrospective nonrandomized comparative studies (NRCS) with at least 750 patients per surgery type, per study. This was consistent with the 2012 report. In contrast to the 2012 VTE report, we also required at least 50 patients in each included study arm (or intervention).

We included published, peer-reviewed articles, conference abstracts and presentations, and studies reported only in the ClinicalTrials.gov Web site. Non-English language publications were extracted by researchers fluent or facile in the published languages. Unavailable publications were included and extracted only from their English language abstract.

Timing

We included studies with any duration of followup. For VTE outcomes, we extracted results at all reported timepoints, but for meta-analyses we preferentially analyzed timepoints closest to 30 days postoperative (as being the most commonly reported timepoint).

Setting

Studies performed in hospital (with or without continuation of intervention or followup after discharge)

Study Selection

We assessed titles and abstracts of citations identified from literature searches for inclusion, using the above eligibility criteria. Abstract screening was done in the open-source, online software Abstrackr (http://abstrackr.cebm.brown.edu/). Full-text articles of potentially relevant abstracts were retrieved and a second review for inclusion was conducted by reapplying the eligibility criteria. Both abstract and full-text screening was conducted in duplicate with conflicts resolved by reconciliation among the whole research team. All rejected full-text articles were confirmed by the project lead.

Studies included in the 2012 VTE report were reassessed for inclusion based on the summarized data available in the 2012 VTE report. In general, we did not confirm eligibility criteria for these studies from the full-text articles.

Data Extraction

Each study was extracted by one methodologist and confirmed by at least one other experienced methodologist. Disagreements were resolved by discussion among the team. Data extraction was conducted into customized forms in the Systematic Review Data Repository (SRDR) online system (http://srdr.ahrq.gov) designed to capture all elements relevant to the KQs. These included population characteristics, including description of patients' surgery, descriptions of the interventions analyzed, descriptions of relevant outcomes, sample sizes, study design features, funding sources, results (including adverse events), and risk of bias assessment. The forms were tested on several studies and revised as necessary. [Upon completion of the review, the SRDR database will be] made accessible to the general public (with capacity to read, download, and comment on data).

New studies added to the 2012 VTE report were extracted from the full-text articles and any available supplemental material. With few exceptions, eligible studies from the 2012 VTE report extracted and entered into SRDR based only on the available data presented in the 2012 VTE report.

Risk of Bias Assessment

We based the methodological quality of each study on predefined criteria. For RCTs, we used the Cochrane risk of bias tool,[14] which asks about risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential biases. For observational studies, we used selected questions from the Newcastle Ottawa Scale about comparability of cohorts, representativeness of the population, and adjustment for different lengths of follow-up.[15] The methodological quality of the eligible studies from the 2012 VTE report was based solely on what was reported in that report's methodological quality tables. Risk of bias questions included in the current review that were not assessed in the 2012 VTE report were marked as "NR" (not reported).

Data Synthesis

Pairwise Meta-Analysis

For KQs 1 through 4 and 6, we conducted restricted maximum likelihood random effects model meta-analyses of four or more comparative studies that were sufficiently similar in population, interventions, and outcomes. Odds ratios (ORs) were chosen as the metric to analyze categorical outcomes. In the analysis of rare outcomes (<1%), we used Peto's OR. [16-18] Studies with no events in both trial arms were excluded as they do not contribute to the estimate of the summary effect. In the analysis by class (KQ 1), for trials containing arms with different doses of the same intervention, we included the arm that was most similar to other studies or the arm with the largest sample size in the event that it was the only study of that intervention. Pairwise meta-analyses were conducted in R using the *metafor* package. Results are presented in terms of summary ORs and the corresponding 95 percent confidence interval (CI).

Network Meta-Analysis

To address KQ 5, we conducted network meta-analyses under a Bayesian framework. Network meta-analysis is an extension of pairwise meta-analyses that simultaneously combines direct comparisons (where interventions are compared head-to-head) and indirect comparisons (where interventions are compared through other reference interventions). Combining the direct and indirect evidence not only improves precision of estimates, but also provides estimates for all pairwise comparisons, including those missing from the direct evidence. The key assumption of the network meta-analysis is that there is consistency of direct and indirect effects. Consistency is likely to hold when the distribution of effect modifiers is similar across trials, and thus, patients are similar across trials. If this assumption is violated, there may be inconsistency between the direct evidence and indirect evidence of treatment comparisons (where the direct and indirect comparisons contradict each other).

For binary outcomes (e.g., total DVT and major bleeding), the network meta-analysis model corresponds to a generalized linear mixed model with a logit link. We included random effects on the treatment parameters, which allowed each study to have a different but related treatment effect estimate versus a reference treatment. The amount of between-study variance (heterogeneity) was assumed to be constant across all treatment comparisons. If these models did not converge, we used a fixed effect model, which sets the between-study variance to 0. We used noninformative prior distributions for the model parameters.

For each analysis, we empirically assessed if the network meta-analysis consistency assumption was violated by comparing the direct and indirect evidence using a node-splitting approach. [19] This approach evaluates each treatment comparison in terms of its direct and indirect evidence estimates. Discrepancies between these estimates indicate inconsistency. Since we did not find any evidence of inconsistency, only results from the (consistency) network meta-analysis are presented.

We conducted a total of 12 network meta-analyses to compare all treatment alternatives across studies. For each of three surgeries (THR, TKR, and HFx surgery) and for the two outcomes (total DVT and major bleeding) we conducted two analyses: 1) comparisons of classes of thromboprophylaxis interventions (e.g., LMWH, antiplatelet drugs) and 2) comparisons of individual interventions. For trials containing arms with different doses of the same intervention, we included the arm that was most similar to other studies or the arm with the largest sample size in the event that it was the only study of that intervention. For all network meta-analyses (in

contrast to KQ 1-4 and 6), we included placebo/no treatment as an intervention (or class) to strengthen the network of evidence. Network meta-analyses were conducted in R using the *gemtc* package. Results are presented in terms of summary ORs and the corresponding 95 percent credible interval (CrI).

Subgroup Analyses and Metaregression

All studies were evaluated for within-study subgroup (or predictor) analyses. As feasible, studies were also categorized based on whether, as a whole, they evaluated particular populations of interest, such as studies that included at least 90 percent of a subgroup of interest, including sex, race/ethnicity, older age group, body weight category, tobacco use, chronic disease, varicocities, history of bleeding disorders or surgical bleeding, prior VTE, presurgical use of antiplatelet drugs or warfarin, or hormones, unilateral versus bilateral surgery, use of cemented fixation, tourniquet use, tranexamic acid use, and anesthesia type. We also investigated potential differences between studies based on industry funding. We aimed to conduct random effects model metaregressions for many variables but data were too sparse to allow meaningful analyses for most.

Grading the Strength of Evidence

We graded the strength of the body of evidence as per the AHRQ methods guide on assessing the strength of evidence.[20] We assessed the strength of evidence for each principal health outcome, as determined with input from the panel of technical experts: total VTE, symptomatic VTE, PE, DVT, and adverse events. Following the standard AHRQ approach, for each intervention and comparison of intervention, and for each outcome, we assessed the number of studies, their study designs, the study limitations (i.e., risk of bias and overall methodological quality), the directness of the evidence to the KQs, the consistency of study results, the precision of any estimates of effect, the likelihood of reporting bias, and the overall findings across studies. Throughout the report, all estimates with 95 percent CI or CrI beyond 0.5 and 2.0 were considered to be imprecise. Based on these assessments, we assigned a strength of evidence rating as being either high, moderate, or low, or there being insufficient evidence to estimate an effect. *A priori,* we determined that specific comparisons with fewer than four analyzable studies provide insufficient evidence to evaluate strength of evidence (in alignment with the decision to conduct pairwise meta-analysis). However, we allowed an exception when three studies all found a statistically significant effect (in the same direction), in which case we assigned a low strength of evidence of an effect. We did not assign a low strength of evidence to trios of studies that all reported no significant difference since these findings were frequently related to lack of statistical power. The data sources, basic study characteristics, and each strength-of-evidence dimensional rating are summarized in a "Strength of Evidence" table detailing our reasoning for arriving at the overall strength of evidence rating.

Peer Review

A draft version of this report is being reviewed by a panel of expert reviewers, including representatives from [pending] and the general public. The reviewers included experts in [pending]. These experts were either directly invited by the EPC or offered comments through a public review process. Revisions of the draft will be made, where appropriate, based on their comments. The draft and final reports [will] also reviewed by the Task Order Officer and an

Associate Editor from another EPC. However, the findings and conclusions are those of the authors, who are responsible for the contents of the report.

Results

Summary of Studies

The literature searches yielded 1481 citations. We rescreened 118 studies included in the 2012 VTE report and 107 references found in relevant existing systematic reviews. Of these, 423 articles were screened in full text, of which 289 were excluded for the reasons listed in Figure 2 and Appendix B. The included 134 studies, 120 RCTs and 14 NRCSs; they provided 81 studies of THR, 54 of TKR, and 12 of HFx surgery. The publication status and sources of the studies are listed in Figure 2. The grey literature searches added no studies.

Studies evaluated the following thromboprophylaxis classes (and combinations thereof): antiplatelet drugs, direct thrombin inhibitors (DTI), factor VIII inhibitors (FEI), factor Xa inhibitors (FXaI), factor XI inhibitors (FXIi), low molecular weight heparin (LMWH), mechanical devices, unfractionated heparin (UFH), and vitamin K antagonists (VKA). The studies evaluated the following specific interventions (and combinations thereof): apixaban, aspirin, dabigatran, dalteparin, darexaban, desirudin, edoxaban, enoxaparin, eribaxaban, flexion devices, fondaprinux, factor XI antisense oligonucleotide (FXIASO), graduated compression stockings (GCS), heparin, intermittent pneumatic compression (IPC), rivaroxaban, seuloparin, TAK422, tinzaparin, venous foot pump (VFP), and warfarin.

We chose the principal outcomes for this review (the various VTE outcomes, major bleeding, and serious adverse events) based on an *a priori* determination of their importance in regards to thromboprophylaxis choice decisionmaking and the high likelihood that these outcomes would be available to to researches of almost all RCTs. However, we found that for most of the outcomes only a minority of studies reported them. Only total DVT was reported by more than 80 percent of the studies (82%), an arbitrary threshold we chose to suggest high risk of reporting bias. In descending order, the remaining principal outcomes were proximal DVT (68% of studies reported), total PE (54%), major bleeding (53%), fatal PE (50%), symptomatic DVT (40%), symptomatic VTE (20%), total VTE (16%), symptomatic PE (16%), and serious adverse events (12%).

Randomized Controlled Trials

Among the RCTs, 59 (51%) reported industry funding, 3 (3%) used materials supplied by industry, 15 (13%) explicitly reported no industry support, and 39 (34%) did not provide funding information.

In general, for the RCTs the risk of bias was low in randomization, allocation concealment, group similarity at baseline, and methods used for outcome assessment. Reporting, compliance with interventions, timing of outcome assessment, and definition of adverse effects were explicitly reported in fewer than half of the RCTs. Fifty-one RCTs had a high risk of bias regarding blinding of patients (in addition, 14 had unclear risk of bias, 1 not reported from the original report[1]), 50 for blinding of healthcare providers (22 unclear, 1 not reported from the

[1] The current review assessed risk of bias domains not consistently addressed by the 2012 VTE report. We did not assess these studies for these risk of bias domains, but instead marked them as "not reported".

original report), and 16 for blinding of outcome assessors (29 unclear). Twenty-three RCTs had a high risk of bias in compliance of intention-to-treat principle in data analysis (8 unclear). Attrition bias was rated high in 19 RCTs (14 unclear).

Nonrandomized Comparative Studies

Overall, we included 14 NRCSs. Six NRCSs evaluated THR, seven TKR, two had separate analyses of THR and TKR, and one evaluated HFx surgery. Two reported industry funding, and the other 12 NRCSs explicitly reported no industry support. In general, the risk of bias was low for incomplete results reporting (2 unclear) and timing of outcome assessments (3 unclear). One NRCS had high risk of bias for adverse event reporting and one was unclear. Similarly, one NRCS had high risk of bias for compliance with interventions and a second was unclear. One NRCS had high risk of bias for patient selection, and a second was unclear. Seven NRCSs had high risk of bias for group similarity at baseline (4 unclear); five for assessment of outcomes (4 unclear). Seven NRCSs had high risk of bias for blinding of outcome assessors, and another five were unclear. Eight had high risk of bias for selective outcome reporting. Full risk of bias evaluations are in Appendix C.

Key Question 1

In patients undergoing major orthopedic surgery, what is the comparative efficacy between classes of thromboprophylaxis interventions on venous thromboembolism outcomes, major bleeding, other adverse events, and treatment adherence?

Note that for all three surgeries, network meta-analyses comparing classes in regard to total DVT and major bleeds are presented under Key Question 5. The results of comparisons with what was deemed to have sufficient evidence are summarized here; other comparisons are noted, but were deemed to have insufficient evidence.

Total Hip Replacement

Key Points

- 44 RCTs and 5 NRCSs compared classes of interventions in patients undergoing THR.
- Pairwise comparisons between classes had sufficient data for only five pairs of classes.
  - LMWH vs. DTI: Overall favors DTI, with lower risk of VTE (total DVT and proximal DVT; moderate to high SOE) and similar risk of major bleeding (high SoE).
  - LMWH vs. FXaI: Overall, favors LMWH, with an unclear difference in effect on risk of VTE (low to moderate SoE of inconsistent results), but lower risk of bleeding with LMWH (high SoE). There were statistically significant differences for total VTE (favoring FXaI), symptomatic VTE (favoring LMWH), and proximal DVT (favoring LMWH), but no significant difference in symptomatic DVT; the inconsistencies in these finding suggest important reporting bias.
  - LMWH vs. UFH: Overall, favors LMWH, with lower risk of VTE (total PE, proximal DVT), but similar risk of total DVT; moderate to high SoE) and lower risk of major bleeding (moderate SoE).

    - LMWH vs. VKA: Overall, an apparent tradeoff in risks with lower risk of total DVT with LMWH (high SoE), similar risks of proximal DVT (low SoE), and lower risk of major bleeding with VKA (high SoE).
    - Mechanical vs. UFH: Overall, unclear. It is unclear which intervention class has higher risk of total DVT (low SoE), UFH results in lower risk of proximal DVT (high SoE), but insufficient evidence regarding adverse events.
    - For all other class comparisons and outcomes there was insufficient evidence.
    - Although studies reasonably should have had data for all VTE-related outcomes and for major bleeding and other serious adverse events, most outcomes were not reported by many studies, resulting in a high risk of reporting bias across the evidence base.
- A within-study subgroup analysis was inconclusive regarding differential risks of bleeding with LMWH and DTI by CKD stage.
- Industry-funded studies had similar finding as other studies. Asian studies had similar findings as non-Asian studies.

Summary Results

Pairwise comparisons between classes had sufficient data for five pairs of classes (**Table A**). For the comparison of **LMWH vs. DTI**, among four RCTs, three favored DTI to prevent total DVT and three favored DTI to prevent proximal DVT. Meta-analysis of the four tirals did not find a significant difference between drug classes regarding major bleeding.

For the comparison of **LMWH versus FXaI**, among 11 RCTs there is high risk of reporting bias for several of the outcomes. Most meta-analyses of VTE outcomes significantly favored FXaI (total VTE [7 RCTs], total DVT [9 RCTs], proximal DVT [10 RCTs]). However, the meta-analysis of symptomatic VTE significantly favored LMWH over FXaI, but the RCTs reporting symptomatic VTE largely did not report other VTE outcomes. The meta-analysis of symptomatic DVT (8 RCTs) was imprecise and found no significant difference between drug classes. Major bleeding was significantly less likely with LMWH (across 9 RCTs), but there was no significant difference in serious adverse events (5 RCTs).

Among 3 RCTs of **LMWH versus mechanical devices**, there was insufficient evidence and it was unclear how the interventions compare.

From 10 RCTs, meta-analyses of **LMWH versus UFH** significantly favored LMWH to prevent total PE (8 RCTs) and proximal DVT (6 RCTs) and to avoid major bleeding (6 RCTs), but showed no statistically significant difference in total DVT (10 RCTs) and symptomatic DVT (4 RCTs that yielded an imprecise estimate).

Meta-analysis of tehe 4 RCTs of LMWH versus VKA found significantly lower rates of major bleeding with VKA. Three of the RCTs favored LMWH to prevent total DVTs. Results for other outcomes were unclear.

Three RCTs evaluated **mechanical devices versus UFH**, favoring VKA to prevent proximal DVTs, but yielding unclear results regarding total DVT.

Other intervention classes compared by fewer studies (with insufficient evidence) included antiplatelet drugs versus VKA, DTI versus FXaI, DTI versus UFH, and FEI versus FXaI.

Table A. Total hip replacement, intervention class vs. class: Summary of "sufficient" evidence

Comparison	Outcome*	SoE Grade	Design: No. Studies (N)	Summary OR (95% CI) or Range of Estimates	Conclusions†
LMWH vs. DTI	DVT, total‡	Moderate	RCT: 3 (4600)	Range 1.14 to 1.52	Favors DTI
	DVT, proximal	High	RCT: 3 (4600)	Range 1.35 to 1.89	Favors DTI
	Bleeding, major‡	High	RCT: 4 (6900)	0.79 (0.55, 1.14)	Does not favor either
	All (benefits vs. harms)		*RCT: 4 (6900)*		*Favors DTI (lower risk VTE, similar risk bleeding)*
LMWH vs. FXaI	VTE, total	Low	RCT: 7 (6389)	1.82 (1.23, 2.71)	Favors FXaI
	VTE, symptomatic	Low	RCT: 6 (5569)	0.52 (0.31, 0.87)	Favors LMWH
	PE, total	Low	RCT: 4 (10080) NRCS: 1 (1056)	Range 0.33 to 1.67	Unclear
	DVT, total‡	Moderate	RCT: 9 (8645) NRCS: 1 (1056)	1.97 (1.42, 2.74)	Favors FXaI
	DVT, symptomatic	Low	RCT: 8 (11253)	0.82 (0.34, 1.97)	Unclear
	DVT, proximal	Moderate	RCT: 10 (9622)	2.40 (1.23, 4.69)	Favors FXaI
	Bleeding, major‡	High	RCT: 9 (11756)	0.72 (0.52, 0.99)	Favors LMWH
	Bleeding, joint	Low	RCT: 3 (8900)	Range 0.50 to 0.89	Unclear
	Serious adverse events	Moderate	RCT: 5 (6727)	0.95 (0.78, 1.17)	Either
	All (benefits vs. harms)		*RCT: 11 (12472)*		*Favors LMWH (unclear VTE effect, lower risk bleeding)*
LMWH vs. UFH	PE, total	High	RCT: 8 (1878)	0.26 (0.13, 0.54)	Favors LMWH
	DVT, total‡	High	RCT: 10 (2219)	0.84 (0.60, 1.18)	Either
	DVT, proximal	Moderate	RCT: 6 (1506)	0.59 (0.38, 0.93)	Favors LMWH
	Bleeding, major‡	Moderate	RCT: 6 (1960)	0.46 (0.23, 0.92)	Favors LMWH
	All (benefits vs. harms)		*RCT: 10 (2387)*		*Favors LMWH (lower risk VTE and bleeding)*
LMWH vs. VKA	DVT, total	High	RCT: 3 (4537)	Range 0.48 to 0.87	Favors LMWH
	DVT, proximal	Low	RCT: 3 (4537)	Range 0.27 to 1.27	Unclear
	Bleeding, major‡	High	RCT: 4 (5332)	1.68 (1.11, 2.53)	Favors VKA
	All (benefits vs. harms)		*RCT: 4 (5332)*		*Tradeoff (LMWH lower risk VTE, VKA lower risk bleeding)*
Mechanical vs. UFH	DVT, total	Low	RCT: 3 (434)	Range 0.18 to 1.00	Unclear
	DVT, proximal	High	RCT: 3 (434)	Range 2.39 to 4.69	Favors UFH
	All (benefits vs. harms)		*RCT: 3 (434)*		*Unclear (UFH lower risk VTE, insufficient for bleeding)*

Pairwise results of comparisons with sufficient evidence (i.e., not graded "insufficient" strength of evidence [SoE]).
Other abbreviations: DTI = direct thrombin inhibitor; DVT = deep vein thrombosis, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin; NRCS = nonrandomized comparative study; OR = odds raio; PE = pulmonary embolism, RCT = randomized controlled trials; UFH = unfractionated heparin; VKA = vitamin K inhibitor; VTE = venothromboembolism.

* Evaluated outcomes included total venothromboembolism (VTE), symptomatic VTE, total pulmonary embolism (PE), fatal PE, symptomatic PE, total deep vein thrombosis (DVT), symptomatic DVT, proximal DVT, postthrombotic syndrome, pulmonary hypertension, major bleeding (total), surgical site or wound bleeding, other major bleeding (specific), surgical site or wound infection, surgical site or wound complications (other than bleeding or infection), heparin-induced thrombocytopenia, mechanical device complications, inferior vena cava filter complications, and other clinically significant adverse events.

† "Unclear" can also be interpreted as no evidence of a difference (in contrast to evidence of no difference).

‡ Also see Key Question 5.

Subgroup Analysis

One RCT reported results for serious bleeding by level of chronic kidney disease (CKD) in a comparison of LMWH and DTI. Event rates were low for all participants (2% in both the desirudin and the enoxaparin arms). They reported that for CKD stage 3B (n=569), more patients experienced a major bleed in the desirudin arm than in the enoxaparin arm, although the difference was not statistically significant (1.8% vs. 0.3%; P = 0.112). For CKD 3A (n=758), the rates were the same (0.3% in both arms). For CKD 1-2 (n=700), DVT rates were also lower in the enoxaparin arm (0.6% vs. 0%).

Studies were generally homogeneous in terms of patient eligibility criteria, such that most studies included all-comers without eligibility restrictions based on demographics, or other major patient or surgery subtypes. While some studies were restricted based on past bleeding history or chronic antiplatelet or VKA use, no RCTs were restricted to the converse populations (only patients with bleeding history or on antithromobotic medication). Thus, across-study comparisons of subgroup factors are limited.

Among THR RCTs, differences between studies based on industry funding was analyzable for only the comparison of LMWH versus UFH. For total DVT, by random effects model metaregresion no significant difference (P=0.51) was found between the eight industry-funded studies (summary OR 0.91, 95% CI 0.59 to 1.41) and the two studies without reported industry support (summary OR 0.71, 95% CI 0.38 to 1.32). Similarly, for major bleeding, no significant difference (P=0.95) was found between the four industry-funded studies (summary OR 0.62, 95% CI 0.13 to 2.93) and the two studies without industry support (summary OR 0.56, 95% CI 0.26 to 1.20).

For the comparison of Asian versus non-Asian RCTs, only the comparison of LMWH versus FXaI was analyzable. For total DVT, no significant difference (P=0.56) was found between the five Asian studies (summary OR 1.63, 95% CI 0.81 to 3.31) and the four non-Asian studies (summary OR 2.08, 95% CI 1.40 to 3.09) by random effects model metaregresion. The non-Asian studies included more patients, largely explaining the difference in statistical significance between the two sets of studies. Overall, the same percentage of Asian and non-Asian study participants had a DVT among these RCTs (4.7%). Similarly, for major bleeding, no significant difference (P=0.16) was found between the four Asian RCTs with major bleeding events (summary OR 1.95, 95% CI 0.46 to 8.22) and the five non-Asian studies (OR 0.68, 95% CI 0.49 to 0.94). Again, the non-Asian studies included more patients, largely explaining the difference in statistical significance between the two sets of studies. The Asian RCTs had relatively few events, with an overall major bleeding rate of 0.7 percent compared to 1.5 percent among all non-Asian RCTs (P=0.041); however, if the European study with an atypically high reported major bleeding rate (3.5%) is excluded, the non-Asian RCTs have a major bleeding rate of 0.9 percent, similar to the reported Asian rate (P=0.59).

Total Knee Replacement

Key Points

- 28 RCTs and 6 NRCSs compared classes of interventions in patients undergoing TKR.
- Pairwise comparisons between classes had sufficient data for meta-analyses for only two pairs of classes.

- LMWH vs. FXaI: Overall, favors FXaI, with lower risk of total DVT (low SoE), but similar risks for other types of VTE (low to moderate SoE) and similar risks of major bleeding and serious adverse events (low SoE).
- LMWH vs. VKA: Overall, an apparent tradeoff in risks with lower risk of total DVT with LMWH (high SoE), similar risks of proximal DVT (low SoE), and lower risk of major bleeding with VKA (low SoE).
- For all other class comparisons and outcomes there was insufficient evidence.
- Although studies reasonably should have had data for all VTE-related outcomes and for major bleeding and other serious adverse events, most outcomes were not reported by many studies, resulting in a high risk of reporting bias across the evidence base.

- A within-study subgroup analysis did not find a substantial difference in relative effect of antiplatelet drug vs. mechanical device between unilateral or bilateral TKR surgery.
- Industry-funded studies had similar finding as other studies. Asian studies had similar findings as non-Asian studies.

Summary Results

Pairwise comparisons between classes had sufficient data for only two pairs of classes (**Table B**). For the comparison of **LMWH versus FXaI**, across 10 RCTs, meta-analysis significantly favored LMWH to prevent total DVT (7 RCTs), but there was no statistically significant difference for total VTE (4 RCTs), symptomatic DVT (8 RCTs), proximal DVT (5 RCTs), major bleeding (7 RCTs), or serious adverse events (4 RCTs).

Among 4 RCTs that compared **LMWH versus VKA**, 3 RCTs favored LMWH to prevent total DVT, 4 RCTs in aggregate did not favor either intervention calss to prevent proximal DVT, and 4 RCTs found lower risk of major bleeding with VKA.

Other intervention classes compared by fewer studies (with insufficient evidence) included antiplatelet drugs versus FXaI, antiplatelet drugs versus mechanical devices, antiplatelet drugs versus VKA, DTI versus FXaI, LMWH versus antiplatelet drugs, LMWH versus DTI, LMWH versus FXIi, LMWH versus mechanical devices, and LMWH versus UFH.

Table B. Total knee replacement, intervention class vs. class: Summary of "sufficient" evidence

Comparison	Outcome*	SoE Grade	Design: No. Studies (N)	Summary OR (95% CI) or Range of Estimates	Conclusions†
LMWH vs. FXaI	VTE, total	Moderate	RCT: 4 (1260)	1.33 (0.89, 1.99)	Either
	DVT, total‡	Low	RCT: 7 (3805)	2.09 (1.70, 2.58)	Favors FXaI
	DVT, symptomatic	Low	RCT: 8 (5715)	0.99 (0.51, 1.91)	Either
	DVT, proximal	Low	RCT: 5 (2011)	1.32 (0.62, 2.82)	Either
	Bleeding, major‡	Low	RCT: 7 (5926)	0.74 (0.42, 1.30)	Either
	Serious adverse events	Low	RCT: 4 (1803)	1.51 (0.80, 2.85)	Either
	All (benefits vs. harms)		*RCT: 10 (6350)*		*Favors FXaI (lower risk DVT, unclear risk bleeding)*
LMWH vs. VKA	DVT, total‡	High	RCT: 3 (1742)	Range 0.42 to 0.67	Favors LMWH
	DVT, proximal	Low	RCT: 4 (1772)	0.51 (0.21, 1.28)	Either
	Bleeding, major‡	Low	RCT: 4 (1960)‡	Range 1.16 to 3.13	Favors VKA
	All (benefits vs. harms)		*RCT: 4 (1960)*		*Tradeoff (LMWH lower risk DVT, VKA lower risk bleeding)*

Pairwise results of comparisons with sufficient evidence (i.e., not graded "insufficient" strength of evidence [SoE]). Other abbreviations: DVT = deep vein thrombosis, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin; OR = odds ratio; RCT = randomized controlled trials; VKA = vitamin K inhibitor; VTE = venothromboembolism.

* Evaluated outcomes included total venothromboembolism (VTE), symptomatic VTE, total pulmonary embolism (PE), fatal PE, symptomatic PE, total deep vein thrombosis (DVT), symptomatic DVT, proximal DVT, postthrombotic syndrome, pulmonary hypertension, major bleeding (total), surgical site or wound bleeding, other major bleeding (specific), surgical site or wound infection, surgical site or wound complications (other than bleeding or infection), heparin-induced thrombocytopenia, mechanical device complications, inferior vena cava filter complications, and other clinically significant adverse events.
† "Unclear" can also be interpreted as no evidence of a difference (in contrast to evidence of no difference).
‡ Also see Key Question 5.

Subgroup Analysis

One RCT compared subgroups of patients who received unilateral or bilateral TKR surgery in a comparison of antiplatelet drug versus mechanical device. They found that in the unilateral group (n=72) the percent of patients with a DVT was lower for those receiving mechanical prophylaxis through a compression boot (22%) compared to those receiving aspirin (47%, P<0.03). In the bilateral group (n=47), DVT incidence was also lower in patients who used compression boots (48%) compared with those who received aspirin (68%), but this difference was not significant (P<0.20). Whether the treatment effect differed between unilateral and bilateral subgroups was not analyzed.

Studies were generally homogeneous in terms of patient eligibility criteria, such that most across-study comparisons of subgroup factors are limited.

Among TKR RCTs, differences between studies based on industry funding was analyzable for only the comparison of LMWH versus FXaI. For total DVT, by random effects model metaregresion no significant difference (P=0.21) was found between the six industry-funded studies (summary OR 2.04, 95% CI 1.68 to 2.49) and the single study without industry support (OR 4.71, 95% CI 1.31 to 16.9).

For the comparison of Asian versus non-Asian RCTs, only the comparison of LMWH versus FXaI was analyzable. For total DVT, no significant difference (P=0.97) was found between the four Asian studies (summary OR 2.15, 95% CI 1.35 to 3.41) and three non-Asian studies (summary OR 2.12, 95% CI 1.59 to 2.82) by random effects model metaregresion. However, the total DVT rate was lower in the Asian RCTs (9.6%) than the non-Asian studies (16.0%, P<0.01). Similarly, for major bleeding, no significant difference (P=0.34) was found between the two Asian studies (summary OR 0.27, 95% CI 0.03 to 2.32) and the five non-Asian studies (OR 0.89, 95% CI 0.29 to 2.72). Major bleeding rates were similar between Asian studies (0.7%) and non-Asian studies (0.9%, P=0.57).

Hip Fracture Surgery

Key Points

- 6 RCTs compared classes of interventions in patients undergoing HFx surgery.
- There is moderate SoE that for LMWH vs. FXaI, LMWH results in a lower risk of total DVT. There is insufficient evidence for all other outcomes for this comparison and for all other intervention class comparisons.

Only 6 RCTs of venoprophylaxis have been conducted comparing intervention classes in patients undergoing HFx surgery. Pairwise comparisons between classes had sufficient data only for the comparison of LMWH versus FXaI (**Table C**). The 3 RCTs that compared **LMWH versus FXaI** found lower risk of total DVT with LMWH, but there was insufficient evidence regarding other outcomes. Other interventions classes compared included antiplatelet drugs

versus mechanical devices, antiplatelet drugs versus VKA, and LMWH versus UFH; there was insufficient evidence regarding these comparisons.

Table C. Hip fracture surgery, intervention class vs. class: Summary of "sufficient evidence"

Comparison	Outcome*	SoE Grade	Design: No. Studies (N)	Summary OR (95% CI) or Range of Estimates	Conclusions†
LMWH vs. FXaI	DVT, total‡	Moderate	RCT: 3 (1816)	Range 2.71 to 3.81	Favors LMWH
	All (benefits vs. harms)		*RCT: 3 (1816)*		*Favors LMWH (LMWH lower risk DVT, insufficient for bleeding)*

Pairwise results of comparisons with sufficient evidence (i.e., not graded "insufficient" strength of evidence [SoE]). Other abbreviations: DVT = deep vein thrombosis, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin; OR = odds ratio; RCT = randomized controlled trials.
* Evaluated outcomes included total venothromboembolism (VTE), symptomatic VTE, total pulmonary embolism (PE), fatal PE, symptomatic PE, total deep vein thrombosis (DVT), symptomatic DVT, proximal DVT, postthrombotic syndrome, pulmonary hypertension, major bleeding (total), surgical site or wound bleeding, other major bleeding (specific), surgical site or wound infection, surgical site or wound complications (other than bleeding or infection), heparin-induced thrombocytopenia, mechanical device complications, inferior vena cava filter complications, and other clinically significant adverse events.
† "Unclear" can also be interpreted as no evidence of a difference (in contrast to evidence of no difference).
‡ Also see Key Question 5.

Key Question 2

In patients undergoing major orthopedic surgery, what is the comparative efficacy of individual thromboprophylaxis interventions within classes on venous thromboembolism outcomes, major bleeding, other adverse events, and treatment adherence?

Note that for all three surgeries, network meta-analyses comparing individual interventions in regard to total DVT and major bleeds are presented under Key Question 5.

Relatively few RCTs of venoprophylaxis compared specific interventions within any given class (3 for THR, 2 for TKR, and 2 for HFx surgery). No comparison was evaluated by more than two studies.

In patients undergoing THR or TKR (in separate analyses), one or two RCTs each evaluated enoxaparin versus semuloparin (LMWHs), enoxaparin versus tinzaparin (LMWHs), and graduated compression stockings versus intermittent pressure devices (mechanical devices). In patients with HFx surgery, one RCT each compared enoxaparin versus dalteparin (LMWHs) and enoxaparin versus semuloparin (LMWHs). Evidence was insufficient to evaluate within-class intervention comparisons.

Key Question 3

In patients undergoing major orthopedic surgery, what is the comparative efficacy of different doses, regimens, or treatment durations of the same thromboprophylaxis interventions on venous thromboembolism outcomes, major bleeding, other adverse events, and treatment adherence?

Key Points

- 22 RCTs and 2 NRCSs compared different intervention doses or durations in patients undergoing THR, 16 RCTs and 1 NRCS in patients undergoing TKR, and 2 RCTs in patients undergoing HFx surgery.

- Only a small number of drug (or class) dose or duration comparisons had sufficient data.
  - THR
    - FXaI low vs. high dose: There is low SoE that high dose FXaI yields a lower risk of total VTE, but insufficient evidence for other outcomes
    - LMWH low vs. high dose: There is moderate SoE that low dose LMWH yields a lower risk of total DVT, but low SoE of an unclear difference to prevent proximal DVT and insufficient evidence for other outcomes.
    - LMWH short vs. long duration: There is moderate to high SoE that long duration LMWH results in lower risk of VTE (total PE, total DVT, and proximal DVT), but insufficient evidence for adverse events.
  - TKR
    - DTI low vs. high dose: There is low SoE that the risk of bleeding is similar with low or high dose DTI, but insufficient evidence for VTE outcomes.
    - FXaI low vs. high dose: There is moderate SoE that high dose FXaI yields a lower risk of total VTE and symptomatic DVT, but that both result in similar risk proximal DVT, and insufficient evidence for adverse events.
  - HFx surgery
    - Data were insufficient to summarize the evidence for different dose or duration of interventions for HFx surgery.

More than 300 specific comparisons of different drug doses or device regimens have been reported; the large majority of specific comparisons were made by a single study only. Comparisons with sufficient evidence are summarized here. These all pertain to class-level analyses; specific intervention comparisons were not evaluated with sufficient frequency to allow a conclusion of sufficient evidence.

Total Hip Replacement

For three pairwise comparisons of dose or treatment duration, there was sufficient data (**Table D**). Five RCTs comparing **FXaI low versus high doses** favored high dose FXaI to prevent total VTE, but the summary OR was not statistically significant.

Five RCTs of **LMWH low versus high doses** significantly favored low dose LMWH to prevent DVT, but it was unclear whethere low or high dose LMWH better prevented proximal DVT (4 RCTs).

Among 6 RCTs of **LMWH short versus long duration treatment**, long duration LMWH resulted in fewer total PE (5 RCTs), but the summary OR was not statistically significant. Long duration LMWH resulted in statistically significantly lower risk of total DVT (6 RCTs) and proximal DVTs (5 RCTs).

Table D. Total hip replacement, comparison of different doses or treatment durations: Summary of "sufficient" evidence

Comparison	Outcome*	SoE Grade	Design: No. Studies (N)	Summary OR (95% CI)	Conclusions†
FXaI low vs. high dose	VTE, total	Low	RCT: 5 (1524)	1.48 (0.92, 2.38)	Favors high dose
LMWH low vs. high dose	DVT, total	Moderate	RCT: 5 (1441)	0.46 (0.28, 0.75)	Favors low dose
	DVT, proximal	Low	RCT: 4 (1047)	0.72 (0.38, 1.36)	Unclear
LMWH short vs. long duration	PE, total	Moderate	RCT: 5 (1128)	2.73 (0.97, 7.64)	Favors long duration
	DVT, total	High	RCT: 6 (1463)	2.87 (2.08, 3.96)	Favors long duration
	DVT, proximal	Moderate	RCT: 5 (1300)	2.94 (1.62, 5.35)	Favors long duration

Pairwise results of comparisons with sufficient evidence (i.e., not graded "insufficient" strength of evidence [SoE]). Other abbreviations: DVT = deep vein thrombosis, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin; OR = odds ratio; RCT = randomized controlled trials.
* Evaluated outcomes included total venothromboembolism (VTE), symptomatic VTE, total pulmonary embolism (PE), fatal PE, symptomatic PE, total deep vein thrombosis (DVT), symptomatic DVT, proximal DVT, postthrombotic syndrome, pulmonary hypertension, major bleeding (total), surgical site or wound bleeding, other major bleeding (specific), surgical site or wound infection, surgical site or wound complications (other than bleeding or infection), heparin-induced thrombocytopenia, mechanical device complications, inferior vena cava filter complications, and other clinically significant adverse events.
† "Unclear" can also be interpreted as no evidence of a difference (in contrast to evidence of no difference).

Total Knee Replacement

For only two pairwise comparisons of dose or treatment duration was there sufficient data (**Table E**). Four RCTs found no significant difference in major bleeding for the comparison of low versus high dose DTI.. Data for other outcomes, including VTE, were insufficient.

Four RCTs that examined relative effectiveness of low versus high doses of FXaI found a statistically significantly lower risk of total VTE and symptomatic DVT with high dose FXaI. The 4 RCTs failed to find a significant difference between low and high dose FXaI to prevent proximal DVTs. Data for other outcomes, including major bleeding, were insufficient.

Table E. Total knee replacement, comparison of different doses or treatment durations: Summary of "sufficient" evidence

Comparison	Outcome*	SoE Grade	Design: No. Studies (N)	Summary OR (95% CI)	Conclusions†
DTI low vs. high dose	Bleeding, major	Low	RCT: 4 (3612)	0.98 (0.50, 1.93)	Either
FXaI low vs. high dose	VTE, total	Moderate	RCT: 4 (775)	2.31 (1.59, 3.35)	Favors high dose
	DVT, symptomatic	Moderate	RCT: 4 (802)	4.76 (1.18, 19.2)	Favors high dose
	DVT, proximal	Moderate	RCT: 4 (779)	2.53 (0.86, 7.47)	Either

Pairwise results of comparisons with sufficient evidence (i.e., not graded "insufficient" strength of evidence [SoE]). Other abbreviations: DVT = deep vein thrombosis, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin; OR = odds ratio; RCT = randomized controlled trials.
* Evaluated outcomes included total venothromboembolism (VTE), symptomatic VTE, total pulmonary embolism (PE), fatal PE, symptomatic PE, total deep vein thrombosis (DVT), symptomatic DVT, proximal DVT, postthrombotic syndrome, pulmonary hypertension, major bleeding (total), surgical site or wound bleeding, other major bleeding (specific), surgical site or wound infection, surgical site or wound complications (other than bleeding or infection), heparin-induced thrombocytopenia, mechanical device complications, inferior vena cava filter complications, and other clinically significant adverse events.
† "Unclear" can also be interpreted as no evidence of a difference (in contrast to evidence of no difference).

Hip Fracture Surgery

One RCT each compared different duration FXaI and LMWH, providing insufficient evidence.

Key Question 4

In patients undergoing major orthopedic surgery, what is the comparative efficacy of combined classes of thromboprophylaxis interventions versus single classes on venous thromboembolism outcomes, major bleeding, other adverse events, and treatment adherence?

Key Points

- 6 RCTs and 2 NRCSs compared single versus combined classes of intervention in patients undergoing THR, 5 RCTs and 3 NRCSs in patients undergoing TKR, and 1 NRCS in patients undergoing HFx surgery.
- Overall, there was insufficient evidence regarding the differences between combined or single classes of interventions to prevent VTE or avoid adverse events.

Note that for all three surgeries, network meta-analyses comparing individual interventions (including combination interventions) in regard to total DVT and major bleeds are presented under Key Question 5. However, in pairwise comparisons, relatively few studies directly compared combination versus single interventions. Most specific comparisons were made by one study only.

For THR, RCTs provided insufficient evidence for comparisons of antiplatelet drug versus antiplatelet drug and mechanical device; LMWH alone versus combinations of LMWH and antiplatelet drug, DTI, FXaI, and mechanical device; mechanical device alone versus the mechanical device and antiplatelet drug, both antiplatelet drug and UFH, and VKA; and UFH alone versus combination UFH and LMWH. In addition, one RCT compared combination antiplatelet drug and UFH versus combination antiplatelet device, UFH, and mechanical device.

Similarly, for TKR, RCTs provided insufficient evidence for comparisons of antiplatelet drug versus combination antiplatelet drug and mechanical device; LMWH alone versus combinations of LMWH and FEI or mechanical device, and UFH alone versus combination UFH and LMWH.

No studies compared single class and combination class interventions after HFx surgery.

Key Question 5

In patients undergoing major orthopedic surgery, based on network meta-analysis, what are the comparative effects of thromboprophylaxis interventions on deep vein thrombosis and, separately, major bleeding?

5.1 What are the comparative effects of different classes of thromboprophylaxis interventions?

5.2 What are the comparative effects of different individual thromboprophylaxis interventions?

Key Points

- Conclusions from all NMAs are limited due to the sparseness of direct comparisons between most interventions within each network.
- For patients undergoing THR, NMA suggests that
  - By class
    - Among 50 RCTs, FXaI is most effective to prevent total DVT, followed by DTI, mechanical devices, LMWH, VKA, and UFH (moderate SoE).
    - Among 30 RCTs, LMWH resulted in fewer major bleeding events than FXaI, and placebo was least likely to cause major bleeding (low SoE).
  - By intervention,
    - Among 50 RCTs, dalteparin is most effective to prevent total DVTs, followed by enoxaparin, (unfractionated) heparin, and, finally, warfarin (moderate SoE).
    - Despite 31 RCTs, comparisons between specific pairs of interventions were too sparse to yield sufficient conclusions regarding risk of major bleeding.

- For patients undergoing either TKR or HFx surgery, comparisons between specific pairs of classes or of intereventions were too sparse to yield sufficient conclusions regarding risks of total DVT or major bleeding.
  - For TKR, 28 RCTs compared classes of interventions for total DVT and 21 compared classes of interventions for major bleeding; 4 RCTs compared specific interventions for total DVT and 22 for major bleeding.
  - For HFx surgery, 6 RCTs compared classes of interventions for total DVT and 21 compared classes of interventions for major bleeding; 8 RCTs compared specific interventions for total DVT and 6 for major bleeding.

Total Hip Replacement

Deep Vein Thrombosis

Comparison of Classes

There were 50 RCTs that evaluated interventions in at least two classes and reported total DVT after THR. Across this study set, 10 classes were evaluated (antiplatelet drugs, DTI, FEI, FXaI, LMWH, LMWH+mechanical, mechanical, UFH, VKA, placebo). Of the 45 possible pairwise comparisons, 17 are covered by direct study comparisons. LMWH was the most common comparator, being directly compared with seven other intervention classes, most frequently with FXaI (9 RCTs), UFH (10 RCTs) and placebo (11 RCTs). Antiplatelet drugs were directly compared with placebo and VKA only; FEI was directly compared with FXaI only.

Overall, the combination of LMWH plus mechanical intervention had the highest probability of being among the top three intervention classes (88%) to prevent DVT in patients undergoing THR, followed by FXaI (85%). The interventions likely to be among the bottom three interventions were placebo (>99%), UFH (87%), and VKA (85%) However, omitting interventions that are directly linked to two or fewer other interventions with two or fewer RCTs each (antiplatelet drugs, FEI, and combined LMWH and mechanical devices), FXaI is most effective to prevent total DVT, followed by DTI, mechanical devices, LMWH, VKA, and UFH.

Comparison of Specific Interventions

In the analysis by drug (or mechanical device), there were 51 RCTs that evaluated at least two interventions and reported total DVT after THR. However, one RCT of TB402 versus rivaroxaban did not connect to the network of evidence and was not included. Across this study set, 18 interventions were evaluated (apixaban, aspirin, dabigatran, dalteparin, darexaban, desirudin, edoxaban, enoxaparin, enoxaparin+GCS, enoxaparin+IPC, fondaparinux, heparin, IPC, semuloparin, tinzaparin, VFP, warfarin, and placebo). Of the 153 possible pairwise comparisons, 30 are covered by direct study comparisons. Enoxaparin was the most common comparator, being directly compared with 14 other interventions; most frequently with heparin (7 RCTs) and placebo (7 RCTs). Dalteparin was directly compared with heparin, warfarin, and placebo only; warfarin was also directly compared with aspirin and IPC; aspirin was also directly compared with placebo.

Overall, the combination of enoxaparin plus IPC had the highest probability of being among the top three interventions to prevent DVT after THR (96%), followed by apixaban (68%). The interventions likely to be among the bottom three interventions were placebo (>99%), warfarin (77%), and tinzaparin (50%) However, omitting interventions that are directly linked to two or fewer other interventions with two or fewer RCTs each (most interventions), dalteparin is most

effective to prevent total DVTs, followed by enoxaparin, (unfractionated) heparin, and, finally, warfarin.

Major Bleeding

Comparison of Classes

There were 30 RCTs that evaluated interventions in at least two classes and reported major bleeding after THR. Across this study set, 9 classes were evaluated (antiplatelet drugs, DTI, FEI, FXaI, LMWH, mechanical, UFH, VKA, placebo). Of the 36 possible pairwise comparisons, 10 are covered by direct study comparisons. LMWH was the most common comparator, being directly compared with six other intervention classes; most frequently with FXaI (9 RCTs), UFH (6 RCTs) and placebo (5 RCTs). Antiplatelet drugs were directly compared with placebo only; FEI was directly compared with FXaI only.

Overall, the mechanical interventions had the highest probability of being among the top three intervention classes (>99%) to avoid major bleeding with thromboprophylaxis after THR, followed by VKA (86%) and placebo (57%). The interventions likely to be among the bottom three interventions were FEI (>99%), UFH (88%), and antiplatelet drugs (67%) However, omitting interventions that are directly linked to two or fewer other interventions with two or fewer RCTs each (all classes except LMWH and FXaI—and placebo), LMWH resulted in fewer major bleeding events than FXaI, and placebo was least likely to cause major bleeding.

Comparison of Specific Interventions

In the analysis by drug (or mechanical device), there were 32 RCTs that evaluated at least two interventions and reported major bleeding after THR. However, one RCT of TB402 versus rivaroxaban did not connect to the network of evidence and was not included. Across this study set, 15 interventions were evaluated (apixaban, aspirin, dabigatran, dalteparin, darexaban, desirudin, edoxaban, enoxaparin, fondaparinux, heparin, IPC, semuloparin, tinzaparin, warfarin, and placebo). Of the 105 possible pairwise comparisons, 20 are covered by direct study comparisons. Enoxaparin was the most common comparator, being directly compared with 12 other interventions; most frequently with heparin (5 RCTs) and placebo (5 RCTs). Dalteparin was directly compared with heparin, warfarin, and edoxaban only; aspirin was directly compared with placebo only.

Overall, IPC had the highest probability of being among the top three interventions (>99%) to avoid major bleeding with thromboprophylaxis after THR, followed by semuloparin (61%). The interventions likely to be among the bottom three interventions were heparin (84%) and aspirin (66%). However, except for LMWH (and placebo) no intervention was directly compared to more than two other interventions by at least two RCTs each.

Total Knee Replacement

Deep Vein Thrombosis

Comparison of Classes

There were 28 RCTs that evaluated interventions in at least two classes and reported total DVT after TKR. Across this study set, 11 classes were evaluated (antiplatelet drugs, antiplatelet drugs + mechanical, DTI, FXaI, FXIi, LMWH, LMWH+mechanical, Mechanical, UFH, VKA, placebo). Of the 55 possible pairwise comparisons, 18 are covered by direct study comparisons.

LMWH was the most common comparator, being directly compared with nine other intervention classes; most frequently with FXaI (7 RCTs). The combination of antiplatelet drugs plus mechanical was directly compared with antiplatelet drugs only.

Overall, FXaI had the highest probability of being among the top three intervention classes (89%) to prevent DVT after TKR, followed closely by the combination of antiplatelet drugs plus mechanical (87%), then DTI (57%). The interventions likely to be among the bottom three interventions were placebo (>99%), antiplatelet drugs (83%), and VKA (82%). However, except for enoxaparin (and placebo) no intervention was directly compared to more than two other interventions by at least two RCTs each.

Comparison of Specific Interventions

In the analysis by drug (or mechanical device), there were 30 RCTs that evaluated at least two interventions and reported total DVT after TKR. Across this study set, 21 interventions were evaluated (apixaban, aspirin, aspirin+VFP, dabigatran, darexaban, edoxaban, enoxaparin, enoxaparin+GCS, enoxaparin+IPC, enoxaparin+VFP, flexion, fondaparinux, FXIASO, heparin, IPC, rivaroxaban, semuloparin, tinzaparin, VFP, warfarin, placebo). Of the 210 possible pairwise comparisons, 32 are covered by direct study comparisons. Enoxaparin was the most common comparator, being directly compared with 16 other interventions. Flexion was directly compared with placebo only; enoxaparin+GCS was directly compared with enoxaparin+IPC only; IPC and aspirin+VFP were directly compared with aspirin only.

Overall, rivaroxaban had the highest probability of being among the top three interventions to prevent DVT after TKR, followed by the combination of enoxaparin plus VFP (66%) and the combination of aspirin plus VFP (59%). The interventions likely to be among the bottom three interventions were the combination of enoxaparin plus GCS (>99%), placebo (77%), and flexion device (67%). However, except for enoxaparin (and placebo) no intervention was directly compared to more than two other interventions by at least two RCTs each.

Major Bleeding

Comparison of Classes

There were 22 RCTs that evaluated interventions in at least two classes and reported major bleeding after TKR. However, one RCT of antiplatelet drugs versus the combination of antiplatelet drugs plus mechanical did not connect to the network of evidence and was not included. Across this study set, 7 classes were evaluated (DTI, FXaI, FXIi, LMWH, UFH, VKA, placebo). Of the 21 possible pairwise comparisons, 9 are covered by direct study comparisons. LMWH was the most common comparator, being directly compared with each of the six other intervention classes; most frequently with FXaI (7 RCTs), DTI (5 RCTs), and VKA (4 RCTs).

Overall, VKA had the highest probability of being among the top three intervention classes (97%) to avoid major bleeding with thromboprophylaxis after TKR. Notably, though the mechanical devices RCTs did not provide major bleeding data. The interventions likely to be among the bottom three interventions were FXaI (75%) and FXIi (67%). However, except for LMWH (and placebo) no intervention was directly compared to more than two other interventions by at least two RCTs each.

Comparison of Specific Interventions

In the analysis by drug (or mechanical device), there were 23 RCTs that evaluated at least two interventions and reported major bleeding after TKR. However, one RCT of aspirin versus

the combination of aspirin plus VFP did not connect to the network of evidence and was not included. Across this study set, 14 interventions were evaluated (apixaban, dabigatran, darexaban, edoxaban, enoxaparin, eribaxaban, fondaparinux, FXIASO, heparin, semuloparin, TAK422, tinzaparin, warfarin, placebo). Of the 91 possible pairwise comparisons, 21 are covered by direct study comparisons. Enoxaparin was the most common comparator, being directly compared with each of the 13 other interventions; most frequently with dabigatran (5 RCTs).

Across all comparisons, there were no statistically significant differences. Overall, FXIASO had the highest probability of being among the top three interventions (67%) to avoid major bleeding with thromboprophylaxis after TKR, followed by eribaxaban (61%). Notably, though the mechanical devices RCTs did not provide major bleeding data. The interventions likely to be among the bottom three interventions were darexaban (98%), fondaparinux (87%) and edoxaban (55%). However, except for enoxaparin no intervention was directly compared to more than two other interventions by at least two RCTs each.

Hip Fracture Surgery

Deep Vein Thrombosis

Comparison of Classes

There were six RCTs that evaluated interventions in at least two classes and reported total DVT after HFx surgery. However, one RCT of antiplatelet drugs versus mechanical did not connect to the network of evidence. Across this study set, four classes were evaluated (FXaI, LMWH, UFH, placebo). Of the six possible pairwise comparisons, four are covered by direct study comparisons. LMWH was directly compared with each of the three other intervention classes; FXaI was also directly compared with placebo.

Overall, FXaI and UFH were likely to be among the top two interventions whereas placebo and LMWH were likely to be among the bottom two interventions. However, data were sparse and only LMWH was directly compared to more than two other interventions by at least two RCTs each (for two comparisons).

Comparison of Specific Interventions

In the analysis by drug (or mechanical device), there were eight RCTs that evaluated at least two interventions and reported total DVT after HFx surgery. One RCT of aspirin versus VFP did not connect to the network of evidence. Across this study set, seven interventions were evaluated (dalteparin, edoxaban, enoxaparin, fondaparinux, heparin, semuloparin, placebo). Of the 21 possible pairwise comparisons, 8 are covered by direct study comparisons. Enoxaparin was the most common comparator, being directly compared with five other interventions. Heparin was directly compared with dalteparin only.

Overall, heparin (99%) and fondaparinux (98%) had the highest probabilities of being among the top three interventions to prevent DVT after HFx surgery, followed by dalteparin (78%). The other three interventions were likely to be among the bottom three interventions: placebo (98%), enoxaparin (93%), and edoxaban (82%) However, no intervention was directly compared to two other interventions by at least two RCTs.

Major Bleeding

Comparison of Classes

There were four RCTs that evaluated interventions in at least two classes and reported major bleeding after HFx surgery. Across this study set, five classes were evaluated (antiplatelet drugs, FXaI, LMWH, VKA, placebo). Of the 10 possible pairwise comparisons, 6 are covered by direct study comparisons. Placebo was the most common comparator, being directly compared with each of the five other intervention classes.

There were no statistically significant differences. Overall, antiplatelet drugs had the highest probability of being among the top two interventions (>99%) to avoid major bleeding with thromboprophylaxis after HFx surgery, followed by VKA (51%). The interventions likely to be among the bottom two interventions were FXaI (98%) and LMWH (98%). However, except for the comparison of LMWH and FXaI, only single RCTs compared intervention classes.

Comparison of Specific Interventions

In the analysis by drug (or mechanical device), there were six RCTs that evaluated at least two interventions and reported major bleeding after HFx surgery. Across this study set, eight interventions were evaluated (aspirin, dalteparin, edoxaban, enoxaparin, fondaparinux, semuloparin, warfarin, and placebo). Of the 28 possible pairwise comparisons, 9 are covered by direct study comparisons. Enoxaparin was the most common comparator, being directly compared with five other interventions. Aspirin and warfarin were directly compared with each other and placebo only.

There were no statistically significant differences. Overall, aspirin had the highest probability of being among the top three interventions (>99%) to avoid major bleeding with thromboprophylaxis after HFx surgery, followed by placebo (96%) and warfarin (96%). The interventions likely to be among the bottom three interventions were semuloparin (87%), fondaparinux (76%), and enoxaparin (73%). However, only enoxaparin and fondaparinux were directly compared by two RCTs.

Key Question 6

In patients undergoing major orthopedic surgery, what is the comparative efficacy of starting pharmacologic thromboprophylaxis at different times (i.e., preoperative, intraoperative, postoperative) on venous thromboembolism outcomes, major bleeding, other adverse events, and treatment adherence?

Only two RCTs compared LMWH started at different times relative to THR surgery. No eligible studies evaluated patients with TKR or HFx surgery. There was insufficient evidence to yield conclusions.

Discussion

A large volume of evidence has been garnered comparing intervention options to prevent venous thromboembolism (VTE) in patients undergoing total hip replacement (THR), total knee replacement (TKR), and hip fracture (HFx) surgery. In total this systematic review addressing comparative effectiveness and harms of drug and mechanical interventions included 120 RCTs

and 14 large NRCSs. However, these studies pertain to three different surgeries and include nine different classes of intervention and 21 specific interventions (plus additional combination of classes/interventions). Furthermore, the studies disproportionately (78%) evaluated LMWH and enoxaparin in particular (60%). In addition, studies differed in regard to the specific VTE outcomes that were reported. Furthermore, the large majority of studies compared different intervention classes (relevant to Key Question 1), but few compared specific interventions within a class (Key Question 2); different doses, regimens, or intervention durations (Key Question 3); combinations of intervention classes (Key Question 4); or different treatment start times (Key Question 6). Therefore, many of the conclusions (answers to the Key Questions) are highly limited due to insufficient evidence. In addition, for most analyses, there is substantial concern about reporting bias (see *Evidence Limitations*, below).

Evidence Summary

Total Hip Replacement

In summary, from direct comparisons for THR the evidence

- favors DTI vs. LMWH to lower risk of DVT with a similar risk of major bleeding (moderate to high SoE)
- favors LMWH vs. FXaI to lower risk of major bleeding (high SoE) but unclear evidence regarding VTE with inconsistent findings likely due to reporting bias (low to moderate SoE)
- favors LMWH vs. UFH with lower risk of VTE (but similar risk of total DVT) and similar risk of major bleeding (moderate to high SoE)
- found a tradeoff between LMWH and VKA such that LMWH lowers risk of DVT but VKA results in fewer episodes of major bleeding (high SoE)
- favors high dose (vs. low dose) FXaI to lower risk of total VTE (low SoE) but with insufficient evidence regarding other VTE and adverse event outcomes
- favors low dose (vs. high dose) LMWH to lower risk of total DVT (moderate SoE) but with unclear or insufficient evidence for other VTE and adverse event outcomes
- favors long duration (vs. short duration) LMWH to lower risk of VTE, but insufficient evidence for adverse events

From network meta-analyses,

- FXaI is most effective to prevent total DVT, followed by DTI, mechanical devices, LMWH, VKA, and UFH (moderate SoE)
- LMWH resulted in fewer major bleeding events than FXaI, and placebo was least likely to cause major bleeding (low SoE)
- dalteparin is most effective to prevent total DVTs, followed by enoxaparin, (unfractionated) heparin, and, finally, warfarin (moderate SoE)
- comparisons between specific pairs of interventions were too sparse to yield sufficient conclusions regarding risk of major bleeding

For other pairwise comparisons of different intervention classes or different within-class doses or treatment duration, there is insufficient evidence. Similarly, there is insufficient evidence to adequately address differences between specific interventions within the same class, comparisons of single versus combination class interventions, or different start times.

Most outcomes were not reported by many studies, resulting in a high risk of reporting bias across the evidence base. A within-study subgroup analysis was inconclusive regarding

differential risks of bleeding with LMWH and DTI by CKD stage. Industry-funded studies had similar finding as other studies. Asian studies had similar findings as non-Asian studies.

Total Knee Replacement

Fewer studies of TKR (than THR) yielded fewer conclusions with sufficient SoE. In summary, from direct comparisons for TKR the evidence

- favors FXaI vs. LMWH to lower risk of total DVT (low SoE) but with similar risks between the two classes for other types of VTE (low to moderate SoE) and similar risks of major bleeding and serious adverse events (low SoE)
- found a tradeoff between LMWH and VKA such that LMWH better lowers risk of total DVT (high SoE), with similar risks of proximal DVT (low SoE), but VKA has a lower risk of major bleeding (low SoE)
- found that high dose FXaI (vs. low dose) yields a lower risk of total VTE and symptomatic DVT (moderate SoE), but both result in similar risk of proximal DVT (moderate SoE), and there is insufficient evidence for adverse events
- found similar risk of bleeding between low and high dose DTI (low SoE), but insufficient evidence regarding VTE outcomes.

For other pairwise comparisons of different intervention classes or different within-class doses or treatment duration, there is insufficient evidence. Similarly, there is insufficient evidence to adequately address differences between specific interventions within the same class, comparisons of single versus combination class interventions, or different start times. The network meta-analyses also produced insufficient evidence to form adequate conclusions.

Most outcomes were not reported by many studies, resulting in a high risk of reporting bias across the evidence base. A within-study subgroup analysis did not find a substantial difference in relative effect of antiplatelet drug vs. mechanical device between unilateral or bilateral TKR surgery. Industry-funded studies had similar finding as other studies. Asian studies had similar findings as non-Asian studies.

Hip Fracture Surgery

Only 12 eligible studies evaluated thromboprophylaxis interventions in patients who underwent HFx surgery. Most specific comparisons were addressed by only one study. There is moderate SoE that LMWH results in lower risk of total DVT than FXaI, but insufficient evidence for other outcomes. For all other comparisons and for all other Key Questions the SoE is insufficient regarding HFx surgery.

Evidence Limitations

As noted in the evidence summary, despite the large number of trials addressing venothromboprophlaxis in patients undergoing major orthopedic surgery, there is inadequate evidence to confidently compare the effectiveness and the major adverse events of the myriad treatment options. As noted, the large majority of evidence pertains to enoxaparin, limiting the ability to compare all interventions. The network meta-analyses provided greater power to compare all intervention classes and all interventions, but the sparseness of direct (within-study) comparisons for many of the interventions meant that meaningful conclusions could be derived for only a small subset of the interventions.

Further hampering evaluation of the trials, studies were not consistent in which specific outcomes were reported. Notably only total DVT was reported by more than 80 percent of the

studies. Only about half of studies reported major bleeding, the principal adverse event of concern for most interventions. Most of the principal VTE outcomes were reported by 50 percent or fewer of the studies. Only one study reported all prinicipal VTE and adverse event outcomes and only two studies reported all VTE outcomes. Full reporting of VTE outcomes and adverse events by trials would have allowed greater SoE for almost all intervention classes and several specific interventions. However, studies arbitrarily or selectively reported specific outcomes. This is highlighted by the comparison of LMWH and FXaI in THR patients where by meta-analysis seven RCTs (with over 6000 patients) found a near double odds of total VTE with LMWH, but six, mostly different RCTs (with over 5000 patients) found double the odds of symptomatic VTE with FXaI. It is reasonably likely that the explanation for the conflicting findings is reporting bias.

Our analyses did not find significant evidence of bias due to industry funding. However, 54 percent of the trials were industry-supported and only 13 percent of RCTs explicitly reported no industry support, which might partially explain the selective reporting.[21,22] The relatively small number of RCTs available for meta-analysis for any given comparison and the small percentage of studies explicitly with no industry support meant that our analyses of industry funded required us to combine RCTs with no industry support and those that did not report funding source. If many of the studies that did not report funding were in fact industry-funded, then any real funding-source bias would have been diluted by the misclassification of funding source.

The RCTs were generally consistent in regard to their eligibility criteria, mostly including all-comers without contraindications. This approach improves the applicability of the individual trials (and thus of the systematic review). Nonetheless, effect sizes in subgroups were rarely reported in these RCTs, and it greatly hampered our ability to evaluate potential explanations for heterogeneity or to hypothesize about possible subgroup differences based on patient history or surgery or anesthesia characteristics. Other than funding source, we were able only to evaluate potential differences between Asian and non-Asian studies. Overall, we found no significant difference between studies conducted in different regions (among analyzable studies), except major bleeding for the comparison of LMWH and FXaI in patients undergoing THR (summary OR in Asian RCTs 1.95, 95% CI 0.46 to 8.22; summary OR in non-Asian studies 0.68, 95% CI 0.49 to 0.94). Nevertheless, the event rates in the Asian studies were generally lower than the non-Asian studies. It suggests incomparability in the two populations besides ethnicity, which might explain the potential difference in the treatment effects. Only two RCTs reported on within-study subgroup analyses based on chronic kidney disease stage (major bleeding, enoxaparin vs. desirudin) and by unilateral versus bilateral TKR surgery (DVT, aspirin vs. compression boots). Neither study found a significant difference in treatment effect in the different subgroups

Future Research Recommendations

Much of the evidence base is insufficient to allow confident conclusions. Much of this lack is due to a relative sparseness of evidence evaluating interventions other than LMWH, and enoxaparin in particular. A more complete evidence base for the other treatments would allow for a stronger ranking of intervention classes, and of specific interventions, in term of risk of VTE and risk of major bleeding (and other adverse events). Currently, there has been substantially more research conducted in patients undergoing THR than TKR; further studies regarding TKR may be warranted. In particular, few RCTs have been conducted in HFx surgery.

To avoid real and perceived bias (including, in particular concerns about reporting bias), ideally, a greater number of studies should be funded independently of industry. Furthermore, to minimize bias, all studies should report the full range of outcomes of interest, regardless of study results. Trial registration *in priori* and standard reporting compliant with Consolidated Standards of Reporting Trials (CONSORT) statement also help reduce potential reporing bias. For VTE prophylaxis studies, there is a fairly standard list of VTE and adverse event outcomes that are generally accepted as being of interest. This systematic review covers a complete list of outcomes that should be reported by all studies. To reduce the risk of bias in systematic reviews, all outcomes, particularly including those with no events, should be reported. This review made no assumptions about unreported event rates. Therefore, since mechanical device studies rarely reported bleeding (or other adverse event) outcomes, our pairwise and network meta-analysis review of mechanical devices had insufficient evidence about risk of bleeding. Ideally, all existing RCTs should report their full set of outcome results. This can relatively easily be done by submitting trial results to a publicly-accessible registry such as ClinicalTrials.gov.

Larger RCTs should evaluate differences in treatment and adverse event effects in relevant subgroups of patients. Ideally, these analyses should be adequately powered. Based on our discussions with a panel of clinical experts and other key informants, the following subgroup analyses are of interest: sex, race/ethnicity, age, body weight, tobacco use, chronic disease, varicocities, history of bleeding disorders or surgical bleeding, prior VTE, presurgical use of antiplatelet drugs or warfarin, or hormones, unilateral versus bilateral surgery, use of cemented fixation, tourniquet use, tranexamic acid use, and anesthesia type. A small number of trials were explicitly limited to some of these subgroups (including no presurgical use of antithrombotics and unilateral surgery), the counterfactuals (e.g., only presurgical antithrombotics or bilateral surgery) have not been studied. Since it is unlikely that RCTs will focus on these rarer and higher-risk factors, it is more important for researchers to evaluate the subgroups within their studies, when available.

Conclusions

While a large body of RCT evidence exists on comparative effectiveness and harms of venothromboprophylaxis interventions after major orthopedic surgery, none of the Key Questions are fully and adequately addressed. The largest body of evidence exists for THR, with fewer studies of TKR, and very few studies of HFx surgery. The large majority of studies evaluated LMWH (enoxaparin, in particular) with relatively few studies evaluating other intervention classes. Only a small minority of studies reported no industry support. Studies did not regularly report on all VTE-related and adverse effect outcomes, resulting in some suggestion of reporting bias. Almost no studies reported subgroup analyses. These limitations restrict the conclusions that can be drawn from the body of evidence.

Briefly, for patients undergoing THR, there is moderate to high SoE that FXaI and DTI are more effective than LMWH and mechanical devices to prevent VTE, which are in turn more effective than UFH and VKA (all as single treatments). FXaI and UFH result in more major bleeding episodes than DTI or LMWH; LMWH results in more major bleeding than VKA.

For patients undergoing TKR, there is low to moderate SoE that FXaI is similar in effect or more effective to prevent VTE than LMWH, with similar risk of major bleeding. LMWH and VKA have similar effect to prevent VTE and LMWH and DTI have similar risks of major bleeding.

For patients undergoing HFx surgery, there is insufficient evidence regarding relative effectiveness or adverse event risk of interventions.

Regarding other Key Questions (beyond comparative effectiveness of intervention classes), there is only sufficient evidence that, after THR dalteparin is most effective to prevent total DVTs, followed by enoxaparin, (unfractionated) heparin, and, finally, warfarin; and that lower dose, but also longer duration, LMWH is more effective to prevent total VTE (than higher dose or shorter duration LMWH), but there is no significant difference between different LMWH doses to prevent proximal DVTs or avoid major bleeding. There is also no significant difference in total VTE between different doses of FXaI. For all other interventions, comparisons, outcomes, and Key Questions there is insufficient evidence.

Future studies, particularly of interventions other than enoxaparin, are needed to address most Key Questions. These studies, and if feasible existing studies, should report all VTE-related and adverse event outcomes. Larger trials should conduct and report subgroup analyses of interest. Ideally, more future studies should be funded independently of industry to avoid real and perceived bias.

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Introduction

Background

Major orthopedic surgery carries a high risk for venous thromboembolism (VTE)—deep vein thrombosis (DVT) and pulmonary embolism (PE).[1] The major orthopedic surgeries of greatest concern include total knee replacement (TKR), total hip replacement (THR), and hip fracture (HFx) surgeries. PE, an obstruction of a pulmonary artery or its branches usually by an embolic thrombus, is potentially life-threatening and can result in chronic complications with generally poor prognosis, such as thromboembolic pulmonary hypertension.[2-4] DVTs are the principal intermediate process necessary for surgery-related PE and increase the risk of PE.[5] In addition, about 5 to 10 percent of patients with symptomatic DVTs develop severe postthrombotic syndrome, which may include venous ulcers, intractable edema, and chronic pain; although, these outcomes may take 10 years or more to develop.[6] Estimates suggest that in the contemporary era about 4.7 percent of patients undergoing major orthopedic surgery would have symptomatic VTE without prophylaxis.[1]

A variety of strategies to prevent VTE are available, including pharmacological (antiplatelet, anticoagulant) and mechanical modalities.[1] Pharmacologic prophylactic treatments include unfractionated heparin (UFH), low molecular weight heparin (LMWH), vitamin K antagonists (VKA), antithrombin III-mediated selective factor Xa inhibitors (ATIII), direct factor Xa inhibitors (FXaI), bivalent and univalent direct thrombin inhibitors (DTI), and antiplatelet agents. Mechanical prophylaxis aims to minimize stasis, the principal putative factor resulting in venous thrombosis. It can be dynamic and intermittent (e.g., intermittent pneumatic compression device [IPC]) or static (e.g., graduated compression stockings [GCS]). The modalities can be used alone or in combination, at variable doses (of drugs) or regimens (of mechanical devices; e.g., different pressure or compression frequency), and for different durations. However, prophylaxis with pharmacologic strategies also has important potential harms (risks) including major bleeding, prosthetic joint infections, and the need for reoperation, which may all lead to death or permanent removal of the prosthetic joint. Mechanical modalities (when used alone), however, are thought to be inferior to pharmacological agents to prevent VTE.

VTE prophylaxis (or "thromboprophylaxis") is now standard of care for patients undergoing major orthopedic surgery. Prophylaxis has been demonstrated to reduce the incidence of symptomatic and asymptomatic DVT (in comparison to placebo or no prophylaxis); however, because of rarity of postoperative PE,[1] the body of randomized controlled trial (RCT) evidence is not adequately powered to demonstrate the effect of prophylaxis on PE. The effect of prophylaxis on DVT risk reduction is generally considered an adequate proxy for likely PE risk reduction, but it remains unknown to what extent reducing the incidence of DVTs impacts the magnitude of any reduction in the incidence of PEs. Nevertheless, avoiding DVT is a clinically worthwhile goal to reduce the incidence of lower extremity venous disease,[7] such as postphlebitic syndrome, venous insufficiency,[8, 9] and phlegmasia cerulean dolens (resulting in edema, pain, and gangrene).[10]

Scope and Key Questions

Scope of the Review

The 2012 Comparative Effectiveness Review on Venous Thromboembolism Prophylaxis in Orthopedic Surgery[11] (hereafter "the 2012 VTE report") addressed many of the uncertainties in

this area, including questions regarding the natural history of VTE, predictors of VTE, and the likelihood that DVTs result in PE in patients undergoing THR, TKR, or HFx surgery; the comparative efficacy of VTE prophylaxis strategies with no VTE prophylaxis, within and between classes of VTE prophylaxis modalities, and duration of VTE prophylaxis in patients undergoing these surgeries; and the efficacy of VTE prophylaxis in nonmajor orthopedic surgeries (knee arthroscopy, surgical repair of lower extremity injuries distal to the hip, and elective spine surgery). The 2012 VTE report included studies published from 1980 through May 2011. It found a general dearth of evidence regarding important clinical outcomes (nonfatal PE, fatal PE, major bleeding, reoperation), but high strength of evidence that pharmacologic VTE prophylaxis reduces the risk of DVT compared to no VTE prophylaxis and increases the risk of minor bleeding. Comparisons of mechanical VTE prophylaxis versus no VTE prophylaxis did not provide strong evidence that mechanical prophylaxis reduced the risk of VTE, including, specifically, DVT. The comparisons of different classes of VTE prophylaxis modalities (e.g., different pharmacologic classes or pharmacologic versus mechanical VTE prophylaxis) provided neither adequate evidence for important clinical outcomes nor strong evidence for other outcomes, including DVT. There were few studies evaluating the new FXaIs. In general, different interventions within classes were not statistically significantly different in their effects on DVT or bleeding. There was not strong evidence for other Key Questions.

We conducted a surveillance review of new studies potentially eligible to update all Key Questions from the 2012 VTE report. The surveillance review is summarized in the online protocol for this review.[12] Briefly, we screened and extracted basic data from abstracts found in PubMed from January 2010 to 16 July 2015. We evaluated the number and characteristics of studies—including RCT, nonrandomized comparative studies, systematic reviews, meta-analyses, and network meta-analyses—of potentially relevant articles. The updated literature search yielded 617 citations. Using the 2012 report's eligibility criteria, 160 articles were of potential interest (based on information available in their abstracts). Of these, 48 were existing systematic reviews, 49 were RCTs, 19 were pooling studies (meta-analysis or otherwise) of previous published or unpublished trials, and 44 were nonrandomized comparative studies (with at least 750 participants per study). We used this information to help determine the scope of the systematic review update. Upon discussion of the current state of the evidence with a panel of technical experts, we determined that a focused update of the 2012 AHRQ report would be of greatest value. The panel included 10 members, including four orthopedic surgeons, two hematologists, one pulmonologist, one pharmacologist, one physical therapist, and one nurse practitioner. Based on their input and the findings of the surveillance review, we focused the update on comparisons between specific prophylaxis interventions; different classes of interventions; different doses, regimens, and treatment durations of interventions; different combinations of interventions; and different timing of starting prophylaxis (in relation to the time of surgery).

Several topics covered in the 2012 VTE report are not updated, including Key Questions related to "natural history" in patients not given thromboprophylaxis and incidence or predictors of VTE and comparing thromboprophylaxis to no thromboprophylaxis. In the modern era, it is rare for patients to not have some form of thromboprophylaxis; therefore, this question is of less clinical interest, and it is unlikely that there will be substantial new evidence regarding these topics. Therefore, these topics (regarding no prophylaxis) are not updated. We also do not update the Key Question evaluating DVT as a proxy (or predictor) for PE, as no new evidence was expected. Finally, all questions related to orthopedic surgeries other than TKR, THR, and HFx

surgery are not updated, since only very limited new studies were found during the surveillance review; thus, conclusions and strength of evidence are unlikely to change compared to the 2012 VTE report.

The objectives for the systematic review are to update the 2012 VTE report focused on the comparative effectiveness (for VTE outcomes and harms) of different thromboprophylaxis interventions for patients undergoing major orthopedic surgery (THR, TKR, and HFx surgery).

Key Questions

The following are the Key Questions addressed by the review:

KQ 1 (update of original KQ 5): In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy between classes of thromboprophylaxis interventions on venous thromboembolism outcomes, treatment adherence, major bleeding, and other adverse events?

KQ 2 (update of original KQ 6): In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy of individual thromboprophylaxis interventions within classes (low molecular weight heparin, factor Xa inhibitors, direct thrombin inhibitors, and mechanical devices) on venous thromboembolism outcomes, treatment adherence, major bleeding, and other adverse events?

KQ 3 (new KQ based on original KQ 8): In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy of different doses, regimens, or treatment durations of the same thromboprophylaxis interventions (low molecular weight heparin, factor Xa inhibitors, direct thrombin inhibitors, and mechanical devices) on venous thromboembolism outcomes, treatment adherence, major bleeding, and other adverse events?

KQ 4 (update of original KQ 7 plus expansion): In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy of combined classes of thromboprophylaxis interventions versus single classes on venous thromboembolism outcomes, treatment adherence, major bleeding, and other adverse events?

KQ 5 (new KQ): In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), based on network meta-analysis, what are the comparative effects of thromboprophylaxis interventions on deep vein thrombosis and, separately, major bleeding?

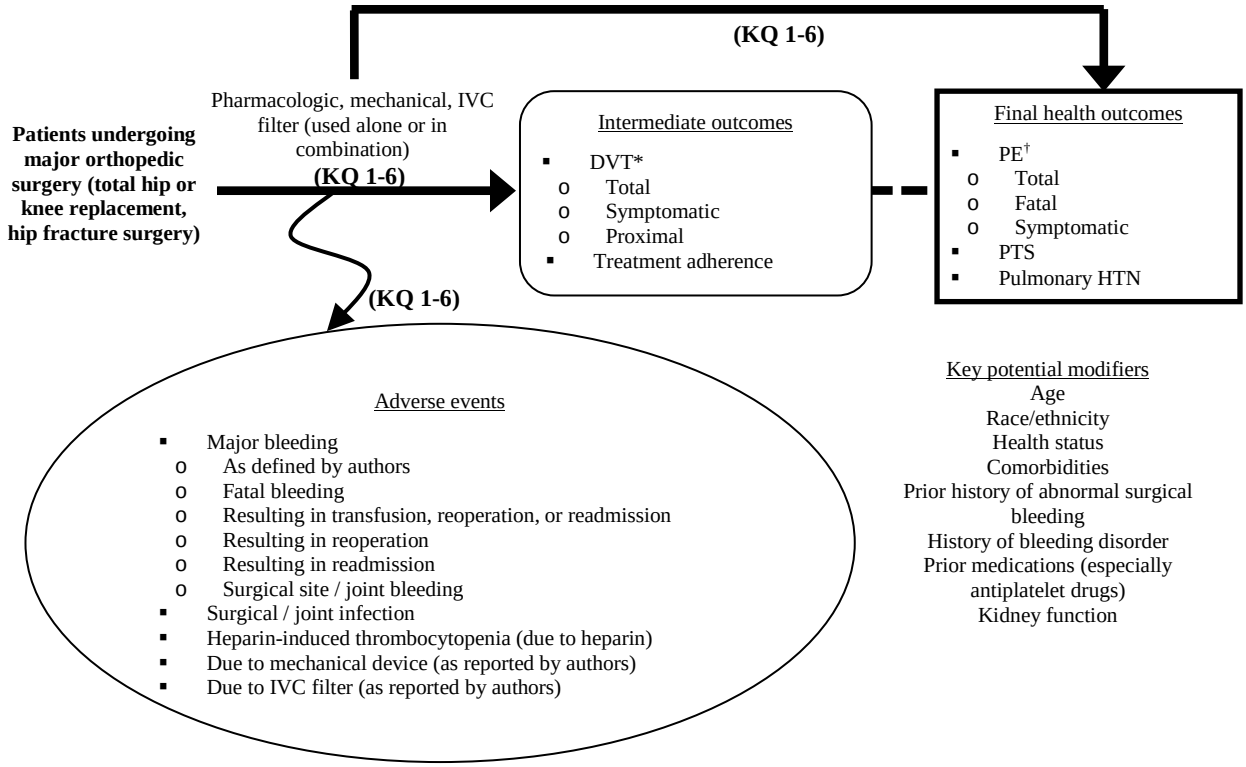
- What are the comparative effects of different classes of thromboprophylaxis interventions?
- What are the comparative effects of different individual thromboprophylaxis interventions?

KQ 6 (new KQ): In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy of starting pharmacologic thromboprophylaxis at different times (i.e., preoperative, intraoperative, postoperative) on venous thromboembolism outcomes, treatment adherence, major bleeding, and other adverse events?

Analytic Framework

To guide the assessment of studies that examine the effect of thromboprophylaxis on final, intermediate, and adverse outcomes in patients undergoing major orthopedic surgery the analytic framework maps the specific linkages associating the populations of interest, the interventions, modifying factors, and outcomes of interest. The analytic framework depicts the chains of logic that evidence must support to link the studied interventions studied.

Figure 1. Analytic framework for the comparative effectiveness of venous thromboembolism prophylaxis in orthopedic surgery



DVT = deep vein thrombosis, HIT = heparin-induced thrombocytopenia, IVC = inferior vena cava, KQ = key question(s), PE = pulmonary embolism, PTS = postthrombotic syndrome, Pulmonary HTN = pulmonary hypertension, VTE = venous thromboembolism

* DVTs are the principal intermediate outcomes necessary for surgery-related PE or postthrombotic syndrome. Total DVTs (asymptomatic and symptomatic, or alternatively, proximal and distal) are of interest because, conceptually, all DVTs may result in PE or postthrombotic syndrome; although, symptomatic DVTs are believed to be a higher risk factor for postthrombotic syndrome and proximal DVTs are believed to be a higher risk factor for PE, particularly fatal PE. Asymptomatic and distal DVTs are not included in the list of DVTs of interest, since they are subsumed by total DVT and are not of great clinical interest alone. Of note, it would be equally reasonable to consider DVTs, especially symptomatic DVTs, to be final health outcomes.

† Total PEs includes both symptomatic and asymptomatic PEs, or alternatively, fatal and nonfatal PEs. Asymptomatic and nonfatal PEs are not included in the list of PEs of interest, since they are subsumed by total PE and are not of great clinical interest alone.

Methods

The present review updates and refines the 2012 Comparative Effectiveness Review on Venous Thromboembolism Prophylaxis in Orthopedic Surgery.[11] It focuses on the Key Questions (KQ) listed at the end of the Introduction. Briefly, it evaluates the comparative effectiveness of different thromboprophylaxis modalities or interventions, not including placebo or no thromboprophylaxis, in patients undergoing major orthopedic surgery—total knee replacement (TKR), total hip replacement (THR), and hip fracture (HFx) surgeries—to prevent venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT) and to minimize major complications, particularly bleeding.

The Brown Evidence-based Practice Center (EPC) conducted the review based on a systematic review of the published scientific literature, using established methodologies as outlined in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[13]

Topic Refinement and Review Protocol

We conducted a surveillance review of the literature since the last search of the 2012 VTE report and discussed our findings with a Technical Expert Panel (TEP) and local domain experts. The TEP provided a range of insights to allow us to refine the KQs, eligibility criteria, and protocol, and regarding the currency and relevance of the 2012 VTE report and its KQs and eligibility criteria. The TEP included 10 members, including four orthopedic surgeons, two hematologists, one pulmonologist, one pharmacologist, one physical therapist, and one nurse practitioner. The panel included committee members from the American Academy of Orthopaedic Surgeons clinical practice guidelines, committee members from the American College of Chest Physicians clinical practice guidelines, and an author of the 2012 VTE report.

Upon revision of the KQs for the updated systematic review, the TEP provided input to help refine the protocol, identify important issues, and define parameters for the review of evidence. The TEP was also asked to suggest additional studies for evaluation.

Search Strategy

A comprehensive search of the scientific literature was conducted to identify relevant studies addressing the KQs that have been published since the 2012 VTE report, which included studies published from 1980 through May 2011. We searched PubMed®, both the Cochrane Central Trials Registry® and Cochrane Database of Systematic Reviews®, and EMBASE® databases. Searches were limited to 2010 through December 23, 2015 [to be updated]. We included an overlap of more than 1 year with the search done for the 2012 VTE report. The updated literature searches replicated the searches from the 2012 VTE report and added additional terms for new treatments (factor Xa inhibitors [FXaI]). See **Appendix A** for the complete search strategy. The search strategy was peer reviewed by an independent, experienced information specialist/librarian.

We also searched the ClinicalTrials.gov registry and the Food and Drug Administration, Healthy Canadians, and the U.K. Medicines & Healthcare products Regulatory Agency Web sites for relevant documents from 2011 through July 27, 2015; no additional studies were found. In addition, the reference lists of published clinical practice guidelines, systematic reviews, and Scientific Information Packages from manufacturers were hand-searched, and the TEP members were invited to provide references of new studies. Existing systematic reviews were used

primarily as sources of new studies. With the exception of studies included in the 2012 VTE report, we extracted and incorporated any studies *de novo* and did not summarize or incorporate the existing systematic reviews. All articles identified through these sources were screened for eligibility using the same criteria as was used for articles identified through literature searches.

All studies cited and tabulated in the 2012 VTE report were screened for eligibility on a par with new studies. However, as noted below, we relied on the summary tables in the 2012 VTE report for data from these studies.

[Peer and public review will provide an additional opportunity for experts in the field and others to ensure that no relevant publications have been missed. The search will be updated in all databases upon submission of the draft report for peer and public review. All summaries and qualitative and quantitative analyses in the update will incorporate all relevant studies, regardless of their source.]

Study Eligibility Criteria

The current eligibility criteria are mostly similar to the criteria used in the 2012 VTE report, as pertain to updated KQs.

Populations of Interest

For all KQs, studies of patients undergoing major orthopedic surgery (THR, TKR, HFx) were eligible. In contrast with the 2012 VTE report, we excluded studies that included more than one type of surgery but did not report results separately by surgery type. This modification was implemented in part for clarity and precision across the three substantially different surgeries and also because of indications of different risks of VTE and major bleeding for the different surgeries, as suggested by the 2012 VTE report (total DVT on placebo: THR 39%, TKR 46%, and HFx surgery 47%; major bleeding on placebo: THR 1%, TKR 3%, and HFx surgery 8%).[1] We did not exclude studies based on details regarding the type of eligible surgery, related anesthesia management, or perioperative care. Subpopulations of interest included those defined by age, race/ethnicity, health status, comorbidities, prior history of abnormal surgical bleeding or bleeding disorder, prior medications (e.g., antiplatelet drugs), kidney function, and treatment adherence/compliance.

Interventions of Interest

The interventions of interest for all KQs included pharmacological VTE prophylaxis agents within the defined classes of oral antiplatelet agents, injectable low molecular weight heparin (LMWH), injectable unfractionated heparin (UFH), injectable or oral factor Xa inhibitors (FXaI), injectable or oral direct thrombin inhibitors (DTI), and oral vitamin K antagonists (VTA), and mechanical VTE prophylaxis devices within the classes graduated compression stockings (GCS), intermittent pneumatic compression devices (IPC), and venous foot pumps (VFP). We also included studies of prophylactic interior vena cava filters for KQs 1 and 5 (that compared classes of interventions). We included multimodality therapies KQ 3 (different doses, regimens, or treatment durations). We included studies of combination therapies (e.g., drug + mechanical prophylaxis) for KQs 4 and 5 and of different starting times relative to surgery for KQ 6.

Comparators of Interest

We included any of the above interventions as comparators as pertinent, including

- KQ 1 intervention in a different class
- KQ 2 intervention within the same class
- KQ 3 same intervention with different (lower) dose (or anticoagulation goal), (less intensive) regimen, or (shorter) duration
- KQ 4 single modality intervention
- KQ 6 same intervention started at different (later) time relative to surgery

There is an important caveat regarding KQ 5, the network meta-analyses. In contrast to other KQs, we included placebo and no thromboprophylaxis study arms. This was done to enhance the power of the network meta-analysis. See below, under Study Design, regarding where no treatment arm data were derived.

Outcomes of Interest

For all KQs, except KQ 5 (the network meta-analysis), we evaluated the following outcomes:

- VTE (combined PE and DVT)
    - Total VTE (symptomatic and asymptomatic)
    - Symptomatic VTE
- PE
    - Total PE (fatal and nonfatal; symptomatic and asymptomatic)
    - Fatal PE
    - Symptomatic PE
- DVT
    - Total DVT (symptomatic and asymptomatic; proximal and distal)
    - Symptomatic DVT
    - Proximal DVT
- Postthrombotic syndrome (PTS)
- Pulmonary hypertension (due to PE)
- Adherence (compliance) with treatment
- Adverse events due to intervention(s)
    - Major bleeding, including:
        - Fatal bleeding
        - Bleeding leading to transfusion
        - Major bleeding leading to reoperation
        - Major bleeding leading to readmission
        - Surgical site / joint bleeding
        - Bleeding leading to infection
        - As defined by authors
    - Surgical site/wound-related infections
    - Surgical site/wound complications (other than bleeding, infection)
    - Heparin-induced thrombocytopenia
    - Adverse events due to mechanical devices (as reported by authors)
    - Adverse events due to IVC filter (as reported by authors)
    - Other clinically significant adverse events reported by studies

For KQ 5 (the network meta-analysis), we evaluated only *total DVT* and *major bleeding*.

We included confirmed and unconfirmed VTE, but downgraded the risk of bias for those studies that analyzed unconfirmed VTE. If both confirmed and unconfirmed VTE were reported, we extracted only the confirmed VTE data.

Study Design

For all KQs, we included randomized controlled trials (RCT) of any sample size. For KQs other than the network meta-analysis (KQ 5), we also included prospective or retrospective nonrandomized comparative studies (NRCS) with at least 750 patients per surgery type, per study. In contrast to the 2012 VTE report, we also required at least 50 patients in each included study arm (or intervention). NRCSs with fewer than 50 patients in any study arm (per surgery type) were still eligible if they compared at least two study arms with ≥50 patients and had ≥750 patients in the remaining study arms; however, the study arms with <50 patients were omitted from analysis.

We included published, peer-reviewed articles, conference abstracts and presentations, and studies reported only in the ClinicalTrials.gov Web site. Non-English language publications were extracted by researchers fluent or facile in the published languages. Unavailable publications were included and extracted only from their English language abstract.

Timing

We included studies with any duration of followup. For VTE outcomes, we extracted results at all reported timepoints, but for meta-analyses we preferentially analyzed timepoints closest to 30 days postoperative (as being the most commonly reported timepoint).

Setting

Studies performed in hospital (with or without continuation of intervention or followup after discharge)

Study Selection

We assessed titles and abstracts of citations identified from literature searches for inclusion, using the above eligibility criteria. Abstract screening was done in the open-source, online software Abstrackr (http://abstrackr.cebm.brown.edu/). Full-text articles of potentially relevant abstracts were retrieved and a second review for inclusion was conducted by reapplying the eligibility criteria. Both abstract and full-text screening was conducted in duplicate with conflicts resolved by reconciliation among the whole research team. All rejected full-text articles were confirmed by the project lead.

Studies included in the 2012 VTE report were reassessed for inclusion based on the summarized data available in the 2012 VTE report. In general, we did not confirm eligibility criteria for these studies from the full-text articles.

Data Extraction

Each study was extracted by one methodologist and confirmed by at least one other experienced methodologist. Disagreements were resolved by discussion among the team. Data extraction was conducted into customized forms in the Systematic Review Data Repository (SRDR) online system (http://srdr.ahrq.gov) designed to capture all elements relevant to the

KQs. These included population characteristics, including description of patients' surgery, descriptions of the interventions analyzed, descriptions of relevant outcomes, sample sizes, study design features, funding sources, results (including adverse events), and risk of bias assessment. The forms were tested on several studies and revised as necessary. [Upon completion of the review, the SRDR database will be] made accessible to the general public (with capacity to read, download, and comment on data).

New studies added to the 2012 VTE report were extracted from the full-text articles and any available supplemental material. With few exceptions, eligible studies from the 2012 VTE report extracted and entered into SRDR based only on the available data presented in the 2012 VTE report.

Risk of Bias Assessment

We based the methodological quality of each study on predefined criteria. For RCTs, we used the Cochrane risk of bias tool,[14] which asks about risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential biases. For observational studies, we used selected questions from the Newcastle Ottawa Scale about comparability of cohorts, representativeness of the population, and adjustment for different lengths of follow-up.[15] The methodological quality of the eligible studies from the 2012 VTE report was based solely on what was reported in that report's methodological quality tables. Risk of bias questions included in the current review that were not assessed in the 2012 VTE report were marked as "NR" (not reported).

Data Synthesis

Narrative and Tabular Synthesis

All included studies are presented in summary tables that include the important features of the study populations, design, intervention, and risk of bias. Study results are summarized in two ways, depending on the available evidence across studies. For specific comparisons that were analyzed by pairwise meta-analysis, results are reported graphically (in forest plots). For specific comparisons, for which pairwise meta-analysis was not appropriate or feasible (i.e., not conducted), outcome results are tabulated in Appendix F and summarized in high-level summary tables. Analyses with sufficient evidence for meta-analysis (including network meta-analysis are described in the text. Other comparisons with inadequate evidence (for meta-analysis and from the perspective of strength of evidence) are summarized more generally. [Upon publication of the final report, all outcome results will be available in SRDR and will be compiled into a simple spreadsheet that will be publically available.]

Pairwise Meta-Analysis

For KQs 1 through 4 and 6, we conducted restricted maximum likelihood random effects model meta-analyses of four or more comparative studies that were sufficiently similar in population, interventions, and outcomes. Odds ratios (ORs) were chosen as the metric to analyze categorical outcomes. In the analysis of rare outcomes (<1%), we used Peto's OR.[16-18] Studies with no events in both trial arms were excluded as they do not contribute to the estimate of the summary effect. In the analysis by class (KQ 1), for trials containing arms with different doses of the same intervention, we included the arm that was most similar to other studies or the arm with

the largest sample size in the event that it was the only study of that intervention. Pairwise meta-analyses were conducted in R using the *metafor* package. Results are presented in terms of summary ORs and the corresponding 95 percent confidence interval (CI).

Network Meta-Analysis

To address KQ 5, we conducted network meta-analyses under a Bayesian framework. Network meta-analysis is an extension of pairwise meta-analyses that simultaneously combines direct comparisons (where interventions are compared head-to-head) and indirect comparisons (where interventions are compared through other reference interventions). Combining the direct and indirect evidence not only improves precision of estimates, but also provides estimates for all pairwise comparisons, including those missing from the direct evidence. The key assumption of the network meta-analysis is that there is consistency of direct and indirect effects. Consistency is likely to hold when the distribution of effect modifiers is similar across trials, and thus, patients are similar across trials. If this assumption is violated, there may be inconsistency between the direct evidence and indirect evidence of treatment comparisons (where the direct and indirect comparisons contradict each other).

For binary outcomes (e.g., total DVT and major bleeding), the network meta-analysis model corresponds to a generalized linear mixed model with a logit link. We included random effects on the treatment parameters, which allowed each study to have a different but related treatment effect estimate versus a reference treatment. The amount of between-study variance (heterogeneity) was assumed to be constant across all treatment comparisons. If these models did not converge, we used a fixed effect model, which sets the between-study variance to 0. We used noninformative prior distributions for the model parameters.

For each analysis, we empirically assessed if the network meta-analysis consistency assumption was violated by comparing the direct and indirect evidence using a node-splitting approach.[19] This approach evaluates each treatment comparison in terms of its direct and indirect evidence estimates. Discrepancies between these estimates indicate inconsistency. Since we did not find any evidence of inconsistency, only results from the (consistency) network meta-analysis are presented.

We conducted a total of 12 network meta-analyses to compare all treatment alternatives across studies. For each of three surgeries (THR, TKR, and HFx surgery) and for the two outcomes (total DVT and major bleeding) we conducted two analyses: 1) comparisons of classes of thromboprophylaxis interventions (e.g., LMWH, antiplatelet drugs) and 2) comparisons of individual interventions. For trials containing arms with different doses of the same intervention, we included the arm that was most similar to other studies or the arm with the largest sample size in the event that it was the only study of that intervention. For all network meta-analyses (in contrast to KQ 1-4 and 6), we included placebo/no treatment as an intervention (or class) to strengthen the network of evidence. Network meta-analyses were conducted in R using the *gemtc* package. Results are presented in terms of summary ORs and the corresponding 95 percent credible interval (CrI).

Subgroup Analyses and Metaregression

All studies were evaluated for within-study subgroup (or predictor) analyses. As feasible, studies were also categorized based on whether, as a whole, they evaluated particular populations of interest, such as studies that included at least 90 percent of a subgroup of interest, including sex, race/ethnicity, older age group, body weight category, tobacco use, chronic disease,

varicocities, history of bleeding disorders or surgical bleeding, prior VTE, presurgical use of antiplatelet drugs or warfarin, or hormones, unilateral versus bilateral surgery, use of cemented fixation, tourniquet use, tranexamic acid use, and anesthesia type. We also investigated potential differences between studies based on industry funding and study region (Asia vs. other). We aimed to conduct random effects model metaregressions for many variables but data were too sparse to allow meaningful analyses for most.

Grading the Strength of Evidence

We graded the strength of the body of evidence as per the AHRQ methods guide on assessing the strength of evidence.[20] We assessed the strength of evidence for each principal health outcome, as determined with input from the panel of technical experts: total VTE, symptomatic VTE, PE, DVT, and adverse events. Following the standard AHRQ approach, for each intervention and comparison of intervention, and for each outcome, we assessed the number of studies, their study designs, the study limitations (i.e., risk of bias and overall methodological quality), the directness of the evidence to the KQs, the consistency of study results, the precision of any estimates of effect, the likelihood of reporting bias, and the overall findings across studies. Based on these assessments, we assigned a strength of evidence rating as being either high, moderate, or low, or there being insufficient evidence to estimate an effect. *A priori*, we determined that specific comparisons with ≤2 analyzable studies provide insufficient evidence to evaluate strength of evidence. In addition, all estimates with 95 percent CI or CrI beyond the arbitrary thresholds of *both* 0.5 and 2.0 were considered to be highly imprecise, resulting in a strength of evidence of "Insufficient" since both very beneficial and very harmful effects are within the effect range. Similarly, if the 95 percent CI or CrI was beyond *both* 0.8 and 1.25, the estimate was considered imprecise and the highest possible strength of evidence was "Low". Due to concerns about reporting bias, for analyses with sufficient data, the SoE was downgraded if <80 percent of the RCTs evaluating a given comparison reported a given outcome (if >1 study missing). The data sources, basic study characteristics, and each strength-of-evidence dimensional rating are summarized in a "Strength of Evidence" table detailing our reasoning for arriving at the overall strength of evidence rating.

Peer Review

A draft version of this report is being reviewed by a panel of expert reviewers, including representatives from [pending] and the general public. The reviewers included experts in [pending]. These experts were either directly invited by the EPC or offered comments through a public review process. Revisions of the draft will be made, where appropriate, based on their comments. The draft and final reports [will] also reviewed by the Task Order Officer and an Associate Editor from another EPC. However, the findings and conclusions are those of the authors, who are responsible for the contents of the report.

Results

The Results chapter is organized first by Key Question, then by surgery—in the following order: total hip replacement (THR), total knee replacement (TKR), and hip fracture (HFx) surgery. Subsequently, results are ordered by comparison in alphabetical order. Comparisons with no evidence (no studies) are omitted. Outcomes are reported in three categories, as follows: 1) venous thromboembolism (VTE) related outcomes—including VTE, pulmonary embolism (PE), deep vein thrombosis (DVT), and other VTE-related outcomes (postthrombotic syndrome [PTS] and pulmonary hypertension [HTN]); 2) adverse events, including major bleeding, other bleeding, serious adverse events (combined), and other adverse events; and 3) adherence. Specific outcomes not reported within each intervention comparison section had no data.

Appendix A presents the literature search strategies (for each searched database). Appendix B lists the articles that were reviewed in full text that were excluded, with their rejection reasons. Appendix C presents the study-level risk of bias assessments of all studies (divided by surgery type for randomized controlled trials [RCT] and then for all nonrandomized comparative studies [NRCS]). Appendix D presents study-level study design and baseline data (divided as in Appendix C). Appendix E presents study-level intervention arm details (also divided as in Appendix C). Appendix F presents study-level results details.

Summary of Studies

The literature searches yielded 1481 citations (**Figure 2**). We rescreened 118 studies included in the 2012 VTE report and 107 references found in relevant existing systematic reviews. Of these, 423 articles were screened in full text, of which 289 were excluded for the reasons listed in Figure 2 and Appendix B. The included 134 studies, 120 RCTs and 14 NRCSs; they provided 81 studies of THR, 54 of TKR, and 12 of HFx surgery. The publication status and sources of the studies are listed in Figure 2. The grey literature searches added no studies.

Studies evaluated the following thromboprophylaxis classes (and combinations thereof): antiplatelet drugs, direct thrombin inhibitors (DTI), factor VIII inhibitors (FEI), factor Xa inhibitors (FXaI), factor XI inhibitors (FXIi), low molecular weight heparin (LMWH), mechanical devices, unfractionated heparin (UFH), and vitamin K antagonists (VKA). The studies evaluated the following specific interventions (and combinations thereof): apixaban, aspirin, dabigatran, dalteparin, darexaban, desirudin, edoxaban, enoxaparin, eribaxaban, flexion devices, fondaprinux, factor XI antisense oligonucleotide (FXIASO), graduated compression stockings (GCS), heparin, intermittent pneumatic compression (IPC), rivaroxaban, seuloparin, TAK422, tinzaparin, venous foot pump (VFP), and warfarin.

We chose the principal outcomes for this review (the various VTE outcomes, major bleeding, and serious adverse events) based on an *a priori* determination of their importance in regards to thromboprophylaxis choice decisionmaking and the high likelihood that these outcomes would be available to to researches of almost all RCTs. However, we found that for most of the outcomes only a minority of studies reported them. Only total DVT was reported by more than 80 percent of the studies (82%), an arbitrary threshold we chose to suggest high risk of reporting bias. In descending order, the remaining principal outcomes were proximal DVT (68% of studies reported), total PE (54%), major bleeding (53%), fatal PE (50%), symptomatic DVT (40%), symptomatic VTE (20%), total VTE (16%), symptomatic PE (16%), and serious adverse events (12%).

Randomized Controlled Trials

Among the RCTs, 59 (51%) reported industry funding, 3 (3%) used materials supplied by industry, 15 (13%) explicitly reported no industry support, and 39 (34%) RCTs did not provide funding information (**Appendix D**).

In general, for the RCTs the risk of bias was low in randomization, allocation concealment, group similarity at baseline, and methods used for outcome assessment. Reporting, compliance with interventions, timing of outcome assessment, and definition of adverse effects were explicitly reported in fewer than half of the RCTs. Fifty-one RCTs had a high risk of bias regarding blinding of patients (in addition, 14 had unclear risk of bias, 1 not reported from the original report[2]), 50 for blinding of healthcare providers (22 unclear, 1 not reported from the original report), and 16 for blinding of outcome assessors (29 unclear). Twenty-three RCTs had a high risk of bias in compliance of intention-to-treat principle in data analysis (8 unclear). Attrition bias was rated high in 19 RCTs (14 unclear). A full list of risk of bias evaluation is available in **Appendix C**.

Nonrandomized Comparative Studies

Overall, we included 14 NRCSs. Six NRCSs evaluated THR,[21-26] seven TKR,[26-32], two had separate analyses of THR and TKR,[33, 34] and one evaluated HFx surgery.[35] Two reported industry funding,[26, 31] and the other 12 NRCSs explicitly reported no industry support (Appendix D). In general, the risk of bias was low for incomplete results reporting (2 unclear) and timing of outcome assessments (3 unclear). One NRCS had high risk of bias for adverse event reporting and one was unclear. Similarly, one NRCS had high risk of bias for compliance with interventions and a second was unclear. One NRCS had high risk of bias for patient selection, and a second was unclear. Seven NRCSs had high risk of bias for group similarity at baseline (4 unclear); five for assessment of outcomes (4 unclear). Seven NRCSs had high risk of bias for blinding of outcome assessors, and another five were unclear. Eight had high risk of bias for selective outcome reporting. Full risk of bias evaluations are in Appendix C.

Subgroup Analyses

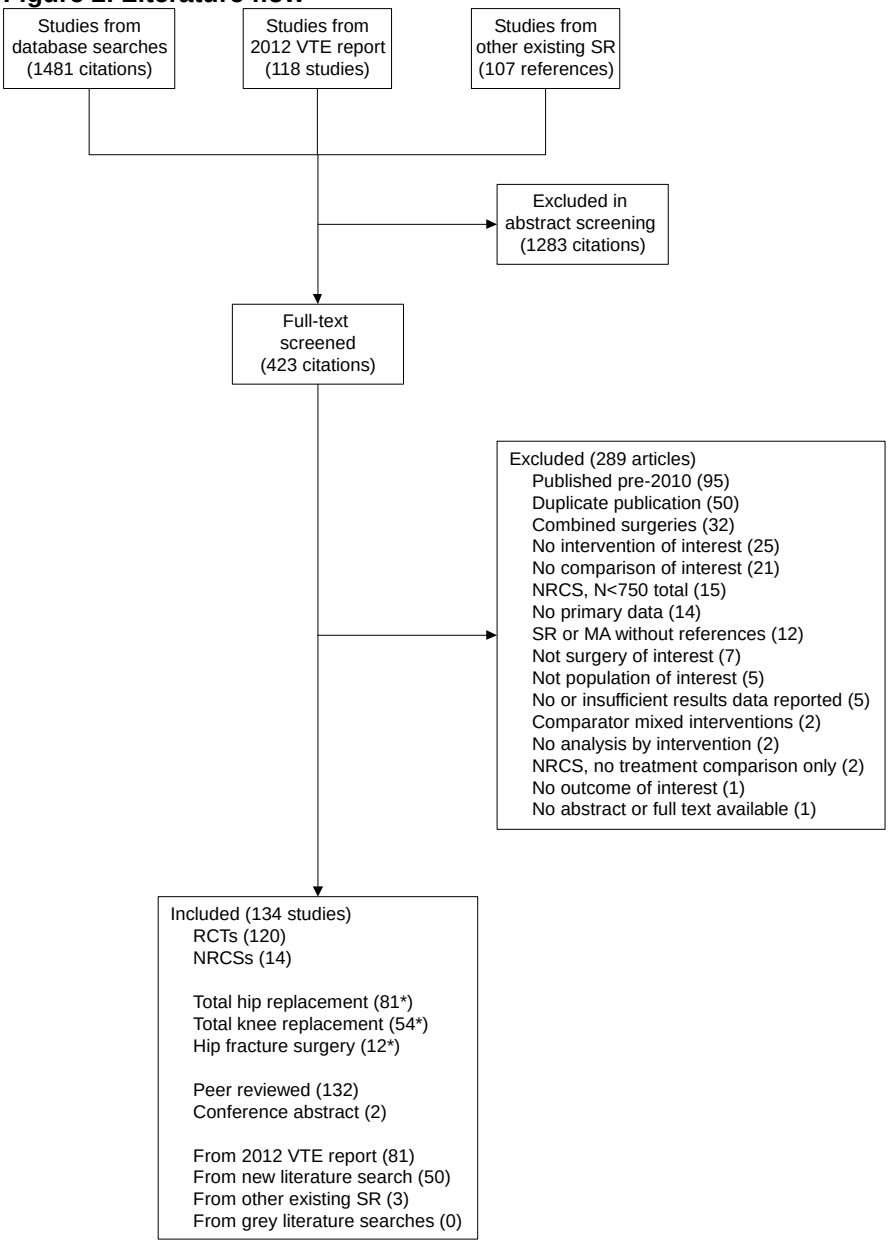
Only two of the RCTs reported subgroup analyses. These are reported in the appropriate sections, based on the Key Question, surgery, and intervention comparison. We collected data to conduct metaregressions across studies based on different population characteristics as listed in the Methods section (under *Subgroup Analyses and Metaregression*). However, overall, studies were generally homogeneous in regard to study eligibility criteria (within surgical types). Almost all studies included all-comers and did not restrict eligibility based on patient or surgery characteristics. Some studies excluded patients with a bleeding history or chronic VKA or antiplatelet drug use, but the counterfactuals (studies that included only patients with a bleeding history or on chronic antithrombosis drugs) were rare or nonexistent. Therefore, analyses across studies of different subgroups were not productive.

For comparisons with at least six studies that could be meta-analyzed (that evaluated the same surgery and the same class or intervention comparison), we conducted metaregressions if at least one of the studies differed in a study-level covariate. Based on the available data, we thus

[2] The current review assessed risk of bias domains not consistently addressed by the 2012 VTE report. We did not assess these studies for these risk of bias domains, but instead marked them as "not reported".

conducted metaregressions for differences in funding source (industry vs. other funding source) and geography (Asian vs. non-Asian study). This latter comparison was conducted due to a perception that risks of VTE and adverse effects may differ in Asian populations.[36]

Figure 2. Literature flow



* Sums to more than 134 since some studies reported different surgeries separately.
Abbreviations: MA = meta-analysis, N=sample size, NRCS = nonrandomized comparative study, RCT = randomized controlled trial, SR = systematic review, VTE = venous thromboembolism.

Key Question 1

In patients undergoing major orthopedic surgery, what is the comparative efficacy between classes of thromboprophylaxis interventions on venous thromboembolism outcomes, major bleeding, other adverse events, and treatment adherence?

Note that for all three surgeries, network meta-analyses comparing classes in regard to total DVT and major bleeds are presented under Key Question 5. The results of comparisons with what was deemed to have sufficient evidence are summarized here; other comparisons are noted, but were deemed to have insufficient evidence.

Total Hip Replacement

The results summary table (**Table X1**) is presented at the end of the THR section. It includes results for all reported comparisons and outcomes from THR RCTs. The reader should refer to this table for each results section summary even though the table is not repeatedly cited in each section. Where data are summarized only appendix tables or are summarized in figures, these are cited.

Antiplatelet Drug Versus VKA

Two RCTs (N=274) and one NRCS (N=887) compared an antiplatelet drug to a VKA;[25, 37, 38] in one RCT a mechanical device was used in all patients. One RCT reported on total and proximal DVTs; the other reported total PE and proximal DVTs. In all analyses, there was no significant difference between intervention classes. The NRCS found a higher rate of bleeding events in the VKA group compared to the antiplatelet group (1.7% vs. 0.3%), without statistical analysis (**Appendix Table F4**).[25] Neither study reported on adherence.

Antiplatelet Drug Versus Mechanical Device

A U.S.-based registry NRCS of 14,657 THR patients found no significant difference in total PE between aspirin and mechanical devices (OR 1.41, 95% CI 0.37 to 5.34), controlling for age, sex, anesthesia risk category, and use of general anesthesia (**Appendix Table F4**).[23]

DTI Versus FXaI

One RCT compared DTI versus FXaI, in which all patients were also treated with LMWH.[39] The study reported only on total DVT, finding no difference between the two intervention classes.

DTI Versus UFH

Two RCTs (N=999) compared DTI versus UFH.[40, 41] Both studies found no significant differences in total PE events and neither reported a fatal PE event. Both found statistically significant differences in total and proximal DVTs, favoring DTI (total DVT: OR 0.26 and 0.44; proximal DVT: OR 0.13 and 0.18).

Neither study reported a fatal bleed. One study found no significant difference in bleeding leading to reoperation and one had no such events. One study found no significant difference in surgical site bleeding. Both studies found no significant difference in 30-day mortality.

Neither study reported on adherence.

FEI Versus FXaI

One RCT (N=415) compared FEI versus FXaI.[42] The study found no significant difference in rates of total VTE, total DVT, and proximal DVT, but no events in either arm for symptomatic VTE, fatal PE, symptomatic PE, or symptomatic DVT.

The study found no significant difference in rate of major bleeding but significantly more surgical site bleeding with FEI. There was no significant difference in 30-day mortality.

The study did not report on adherence.

LMWH Versus Antiplatelet Drug

Two NRCSs compared LMWH with an antiplatelet drug **(Appendix Table F4)**.[22, 23] Both evaluated total PE. One reported no significant difference in total PE, but the other found a higher PE rate in the antiplatelet drug group (1.7%) than the LMWH group (0.2%), without statistical analysis. One of the NRCSs found no significant difference in total DVT or major bleeding events.

LMWH Versus DTI

Four RCTs (N=6900) compared LMWH versus DTI.[43-46] All reported on VTE-related outcomes.

VTE Outcomes

No VTE-related outcome was analyzed by more than three RCTs. One study found no significant difference in symptomatic VTE.[44] Two studies found no significant differences in total PEs or fatal PEs (one study had no fatal PE events).[43, 45] Three studies analyzed total DVT; all found more total DVTs with LMWH, but the difference was statistically significant in only one study (range of ORs: 1.14 [95% CI 0.79 to 1.64] to 1.52 [95% CI 1.19 to 1.94]).[43, 44, 46] The same three studies found similar results for proximal DVT (range of ORs: 1.35 [95% CI 0.53 to 3.42] to 1.89 [95% CI 1.04 to 3.44]). Two of the studies found no significant difference in symptomatic DVT events.[43, 44, 46]

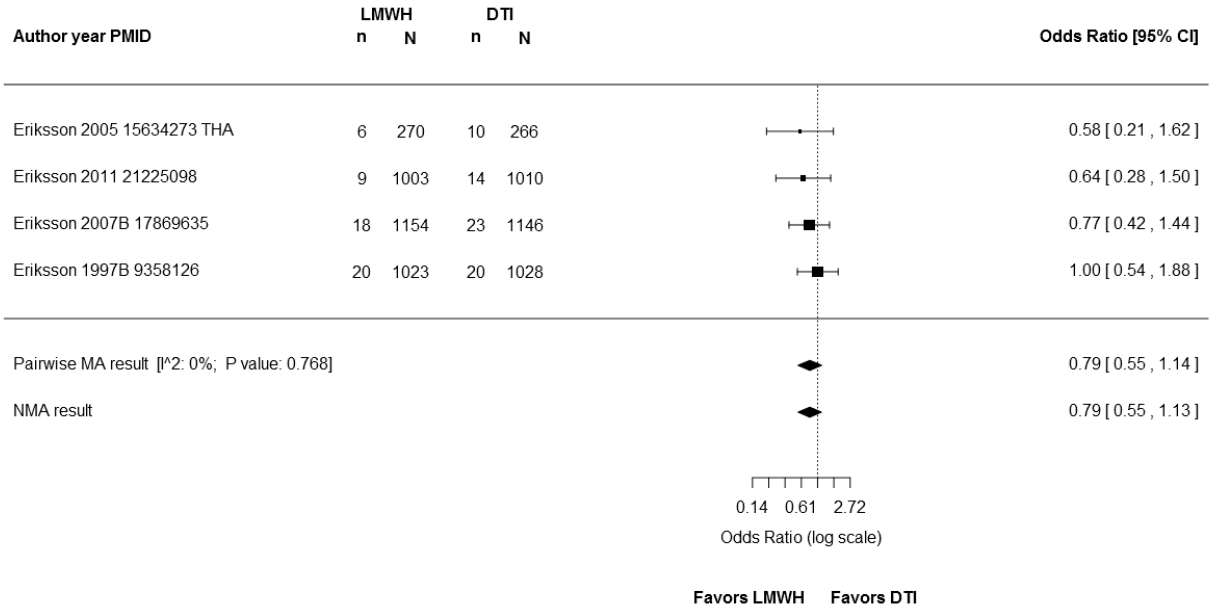
Major Bleeding

Four RCTs (N=6900) that compared LMWH and DTI reported major bleeding (0.9-2.2% in LMWH, 1.4-3.8% in DTI).[43-46] The rate was lower in the LMWH group in three RCTs.[44-46] Meta-analysis of the four RCTs found no significant difference between the two drug classes for the risk of major bleeding (summary OR=0.79; 95% CI 0.55 to 1.14). Study results were homogeneous (I^2 = 0%, P = 0.77) (**Figure 1.thr.1**).

Subgroup Analysis

One RCT reported results for serious bleeding by level of chronic kidney disease (CKD).[43, 47] Event rates were low for all participants (2% in both the enoxaparin and desirudin arms). They reported that for CKD stage 3B (n=569), more patients experienced a major bleed in the desirudin arm than in the enoxaparin arm, although the difference was not statistically significant (1.8% vs. 0.3%; P = 0.11). For CKD 3A (n=758), the rates were the same (0.3% in both arms). For CKD 1-2 (n=700), DVT rates were also lower in the enoxaparin arm (0.6% vs. 0%).[47]

Figure 1.thr.1. Forest plot: Major bleeding, LMWH vs. DTI



Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result) and equivalent summary estimate from corresponding network meta-analysis (NMA). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: DTI = direct thrombin inhibitor, LMWH = low molecular weight heparin, PMID = PubMed identifier.

Other Adverse Events

Two RCTs evaluated fatal bleeding;[44, 45] one found no significant difference, one had no fatal bleeding events. One study each found no significant difference in bleeding leading to reoperation or surgical site bleeding. Three RCTs found no significant difference in 30-day mortality (range of ORs: 0.14 [95% CI 0.01 to 2.75] to 3.03 [95% CI 0.12 to 74.5]).[43-45]

Adherence

No study reported on adherence.

LMWH Versus FXaI

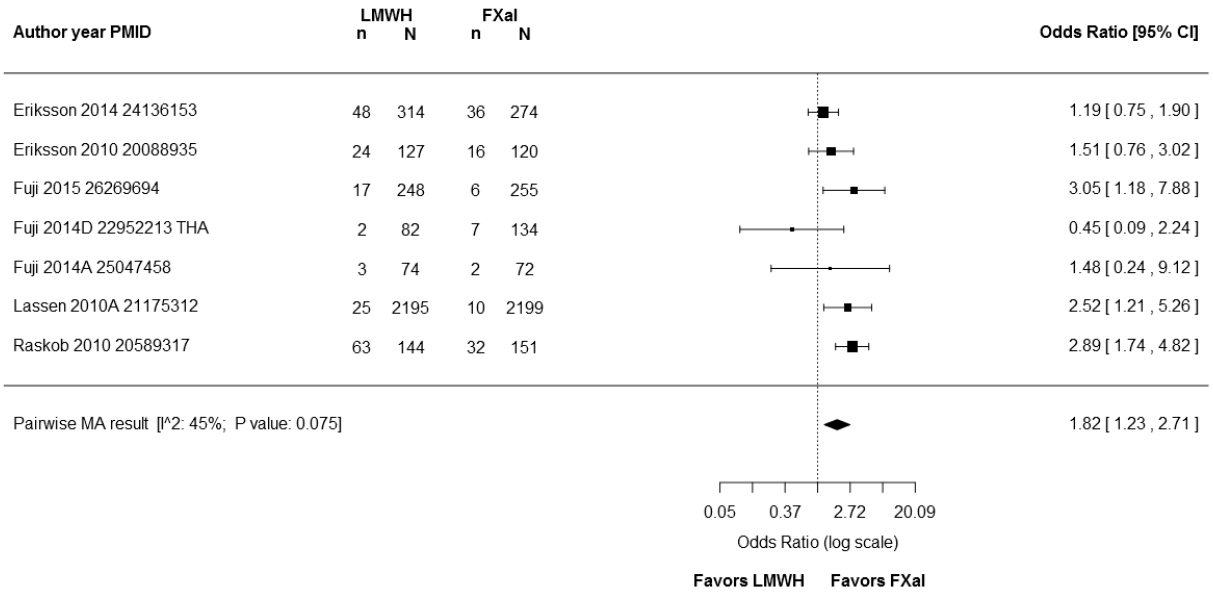
Eleven RCTs (N=12,472) compared LMWH versus FXaI[48-58]; one NRCS also evaluated this comparison.[21] All 12 studies reported on VTE-related outcomes.

Total VTE

Seven RCTs (N=6389) compared LMWH and FXaI and reported the occurrence of total VTE (1.1-43.8% in LMWH, 0.5-21.2% in FXaI).[48-52, 56, 58] The rate was significantly lower in the FXaI group in three RCTs.[48, 56, 58] Meta-analysis of the seven RCTs yielded a summary OR of 1.82 (95% CI 1.23 to 2.71) for the risk of total VTE, significantly favoring FXaI. Significant heterogeneity was shown across the seven RCTs (I^2 = 45%, P = 0.075) (**Figure 1.thr.2**). No clear

explanation of the statistical heterogeneity could be found; however, specific drugs, doses, and regimens varied across RCTs.

Figure 1.thr.2. Forest plot: Total VTE, LMWH vs. FXaI

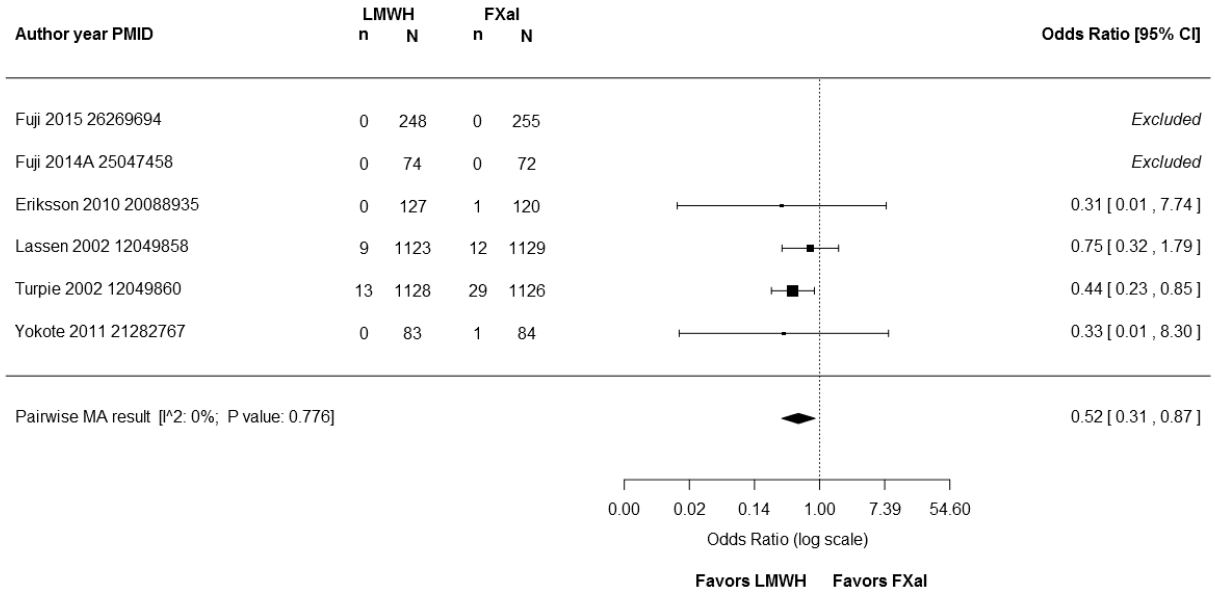


Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, PMID = PubMed identifier.

Symptomatic VTE

Six RCTs (N=5569) reported on symptomatic VTE for comparisons of LMWH and FXaI (0-1.2% in LMWH, 0-2.6% in FXaI).[48, 50, 52, 54, 55, 57] The rate was lower in the FXaI group in four RCTs,[52, 54, 55, 57] statistically significant so in one.[55] Two RCTs[48, 50] reported no occurrence of symptomatic VTE in either group. Meta-analysis of the other four RCTs yielded a summary OR of 0.52 (95% CI 0.31 to 0.87) for the risk of symptomatic VTE, significantly favoring FXaI. Study results were homogeneous (I^2 = 0%, P = 0.78) (**Figure 1.thr.3**).

Figure 1.thr.3. Forest plot: Symptomatic VTE, LMWH vs. FXaI

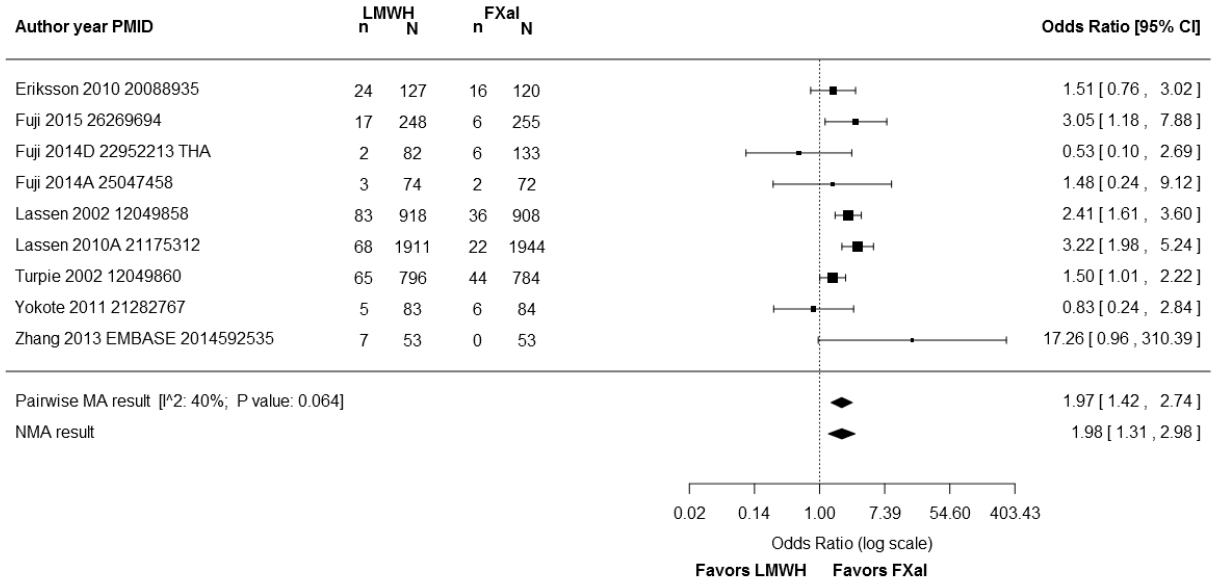


Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, PMID = PubMed identifier.

Total DVT

Nine RCTs (N=8645) that compared LMWH and FXaI reported total DVT (2.4-18.9% in LMWH, 0-13.3% in FXaI).[48-50, 52, 54, 55, 57-59] The rate was significantly lower in the FXaI group in four RCTs.[48, 55, 57, 58] Meta-analysis of the nine RCTs yielded a summary OR of 1.97 (95% CI 1.42 to 2.74) for the risk of total DVT, significantly favoring FXaI. There was significant heterogeneity across the RCTs (I^2 = 40%, P = 0.064) (**Figure 1.thr.4**). No clear explanation of the statistical heterogeneity could be found; however, specific drugs, doses, and regimens varied across RCTs. A single NRCS found no significant difference between intervention classes (**Appendix Table F4**).[21]

Figure 1.thr.4. Forest plot: Total DVT, LMWH vs. FXaI

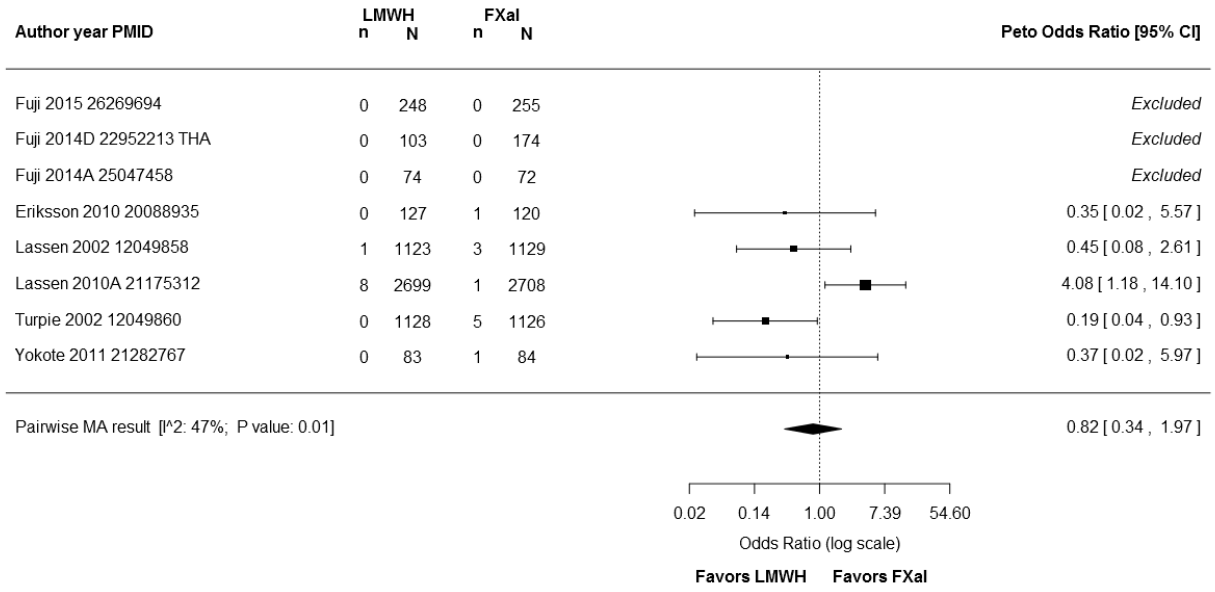


Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result) and equivalent summary estimate from corresponding network meta-analysis (NMA). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, PMID = PubMed identifier.

Symptomatic DVT

Eight RCTs (N=11,253) that assessed LMWH and FXaI reported symptomatic DVT (0-0.3% in LMWH, 0-1.2% in FXaI).[48-50, 52, 54, 55, 57, 58] Patients who received LMWH had a lower rate in four RCTs.[52, 54, 55, 57] Three RCTs[48-50] had no patients with symptomatic DVT in either study arm. Meta-analysis of the other five RCTs found an imprecise estimate of OR with no significant difference between the two drug classes for the risk of symptomatic DVT (summary OR=0.82; 95% CI 0.34 to 1.97). There was significant statistical heterogeneity across the RCTs (I^2 = 47%, P = 0.01) (**Figure 1.thr.5**). No clear explanation of the statistical heterogeneity could be found; however, specific drugs, doses, and regimens varied across RCTs.

Figure 1.thr.5. Forest plot: Symptomatic DVT, LMWH vs. FXaI

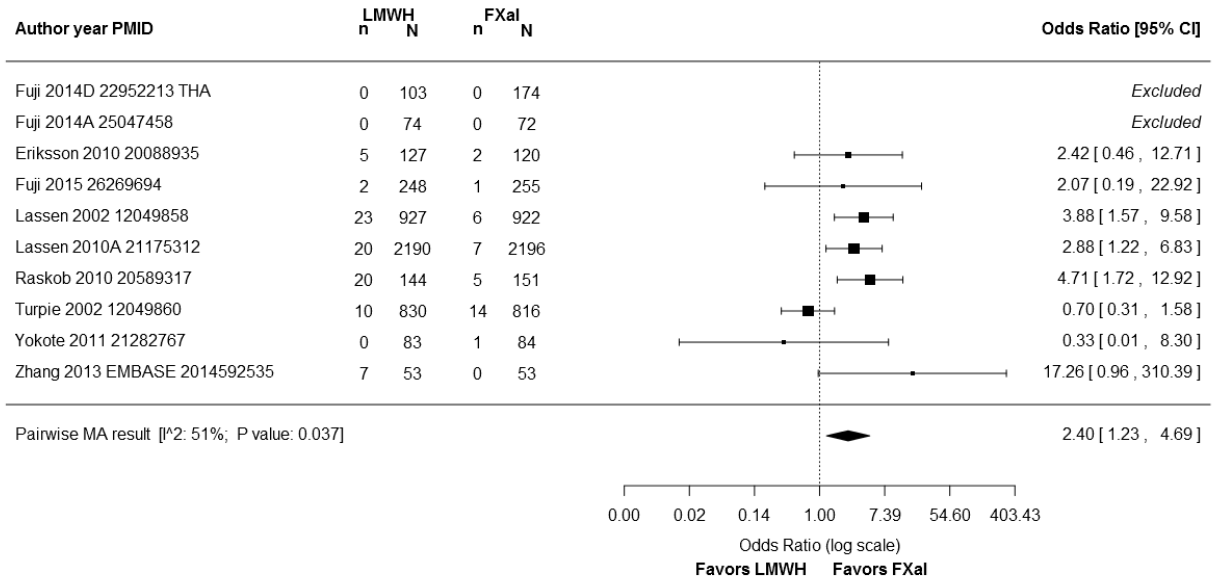


Forest plot of randomized controlled trials with calculated Peto odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with Peto fixed effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, PMID = PubMed identifier.

Proximal DVT

Ten RCTs (N=9622) comparing LMWH and FXaI reported proximal DVT (0-13.9% in LMWH, 0-3.3% in FXaI).[48-50, 52, 54-59] The rate was significantly lower in patients who received FXaI in three RCTs.[56-58] Two RCTs reported no proximal DVT in either comparison group.[49, 50] Meta-analysis of the other eight RCTs yielded a summary OR of 2.40 (95% CI 1.23 to 4.69), finding a significantly lower risk of proximal DVT in the FXaI group. Significant heterogeneity was shown across the RCTs (I^2 = 51%, P = 0.037) (**Figure 1.thr.6**). No clear explanation of the statistical heterogeneity could be found; however, specific drugs, doses, and regimens varied across RCTs.

Figure 1.thr.6. Forest plot: Proximal DVT, LMWH vs. FXaI



Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, PMID = PubMed identifier.

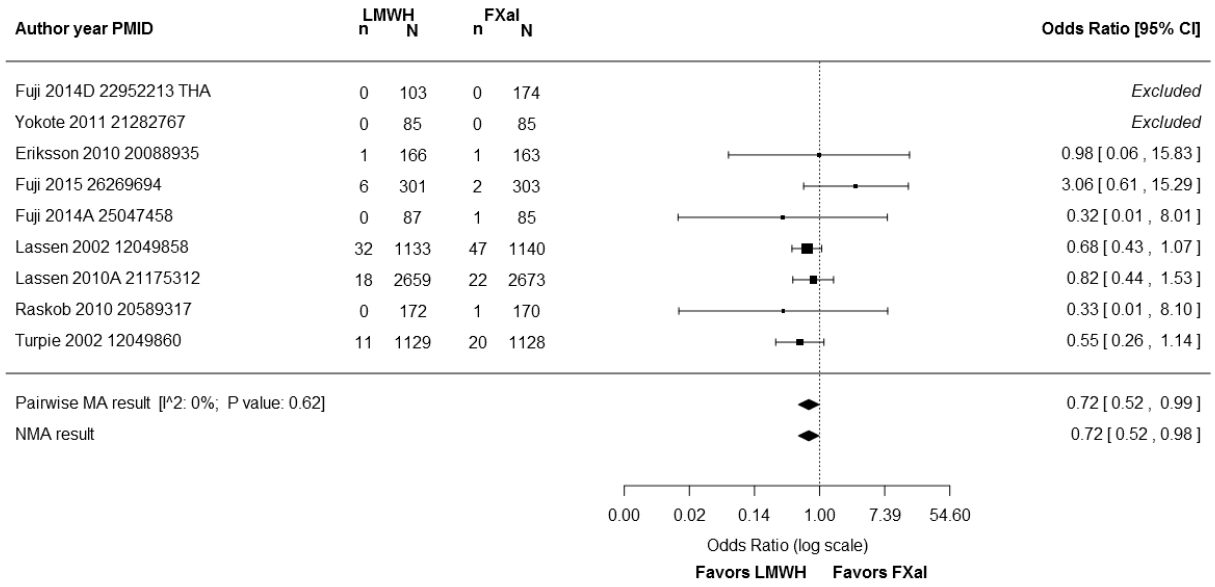
Other VTE Outcomes

Four RCTs[54, 55, 57, 58] and one NRCS[21] reported on total PE, but there were no PE events in one RCT and in the NRCS. Among the remaining three studies, no significant differences were found (range of ORs: 0.33 [95% CI 0.11 to 1.03] to 1.67 [95% CI 0.40 to 7.01]). Eight studies[48, 50-52, 54, 55, 57, 58] reported on fatal PEs, but only two studies had fatal PE events; the two studies found no significant differences (range of ORs: 0.33 [95% CI 0.01 to 8.21] to 2.00 [95% CI 0.18 to 22.1]). Similarly, five studies reported on symptomatic PEs, but only one study had symptomatic PE events, finding no significant difference between intervention classes.

Major Bleeding

Nine RCTs (N=11,756) reported major bleeding for the comparison of LMWH and FXaI (0-2.8% in LMWH, 0-4.1% in FXaI).[48-50, 52, 54-58] The rate was lower in the LMWH group in six RCTs.[50, 52, 55-58] Two RCTs[49, 54] reported no major bleeding in either comparison group. Meta-analysis of the remaining seven RCTs yielded a just-significant difference between the two classes for the risk of major bleeding (summary OR=0.72; 95% CI 0.52 to 0.99), favoring LMWH. Study results were homogeneous (I^2 = 0%, P = 0.62) (**Figure 1.thr.7**).

Figure 1.thr.7. Forest plot: Major bleeding, LMWH vs. FXaI



Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result) and equivalent summary estimate from corresponding network meta-analysis (NMA). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, PMID = PubMed identifier.

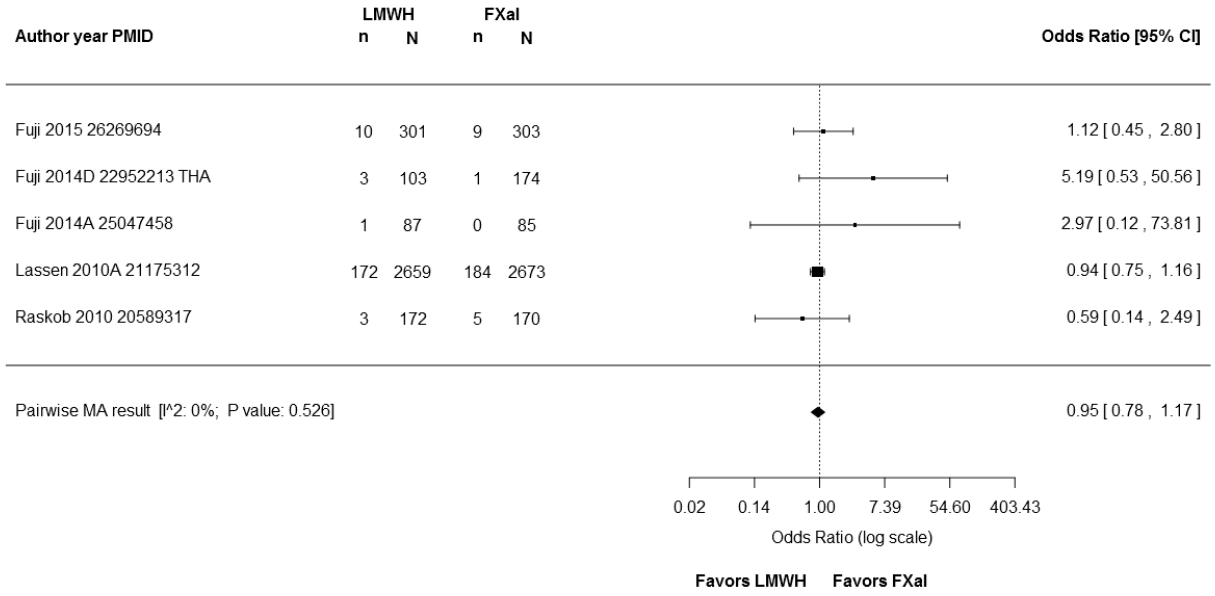
Other Bleeding Events

Three RCTs reported that no patients had fatal bleeding events.[55, 57, 58] The three RCTs reported no significant difference in bleeding leading to reoperation (range of ORs: 0.60 [95% CI 0.14 to 2.53] to 1.01 [95% CI 0.06 to 16.1]).[55, 57, 58] Similarly, three studies reported no significant difference in surgical site bleeding (range of ORs: 0.50 [95% CI 0.12 to 2.00] to 0.89 [95% CI 0.45 to 1.75]).

Serious Adverse Events

Five RCTs (N=6727) comparing LMWH versus FXaI reported serious adverse events (1.2-6.5% in LMWH, 0-6.9% in FXaI).[48, 49, 56, 58, 60] Two studies reported a lower rate in the LMWH group.[56, 58] No significant difference was shown in the meta-analysis of the five studies for the risk of serious adverse events between the two drug classes (summary OR=0.95, 95% CI 0.78 to 1.17). Study results were homogeneous (I^2 = 0%, P = 0.53) (**Figure 1.thr.8**).

Figure 1.thr.8. Forest plot: Serious adverse events, LMWH vs. FXaI



Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, PMID = PubMed identifier.

Other Adverse Events

Three RCTs reported on 30-day mortality,[49, 55, 57] but one had no mortality events; the remaining two studies found no significant difference between intervention classes.

Adherence

Two RCTs found conflicting results regarding adherence.[50, 58] One study found significantly better adherence with LMWH (OR 2.64, 95% CI 1.35 to 5.14); one study found no significant difference, nominally favoring FXaI (OR 0.11, 95% CI 0.01 to 2.05).

LMWH Versus Mechanical Devices

Three RCTs (N=732) compared LMWH versus mechanical devices.[61-63] No significant differences were found for VTE outcomes. One RCT found no significant difference in total VTE. One RCT each found no significant differences in total PE or symptomatic PE. A U.S.-based registry NRCS of 14,657 THR patients found no significant difference in total PE between mechanical devices and LMWH (OR 1.20, 95% CI 0.46 to 3.53), controlling for age, sex, anesthesia risk category, and use of general anesthesia (**Appendix Table F4**).[23] Two RCTs had no fatal PEs. Three studies found no significant differences in total DVT (range of ORs: 0.70 [95% CI 0.36 to 1.36] to 1.03 [95% CI 0.38 to 2.81]). The same three studies found no significant differences in proximal DVTs (range of ORs: 0.67 [95% CI 0.31 to 1.45] to 1.00

[95% CI 0.06 to 16.9]). Two studies reported on proximal DVTs; one had no proximal DVT events and the other found no significant difference in event rates.

One study found much more frequent major bleeding with LMWH than mechanical devices (11/194 vs. 0/198; OR 24.9, 95% CI 1.46, 425),[62] but no significant difference in total serious adverse events. Another study had no fatal bleeding events or 30-day deaths.

No study reported on adherence.

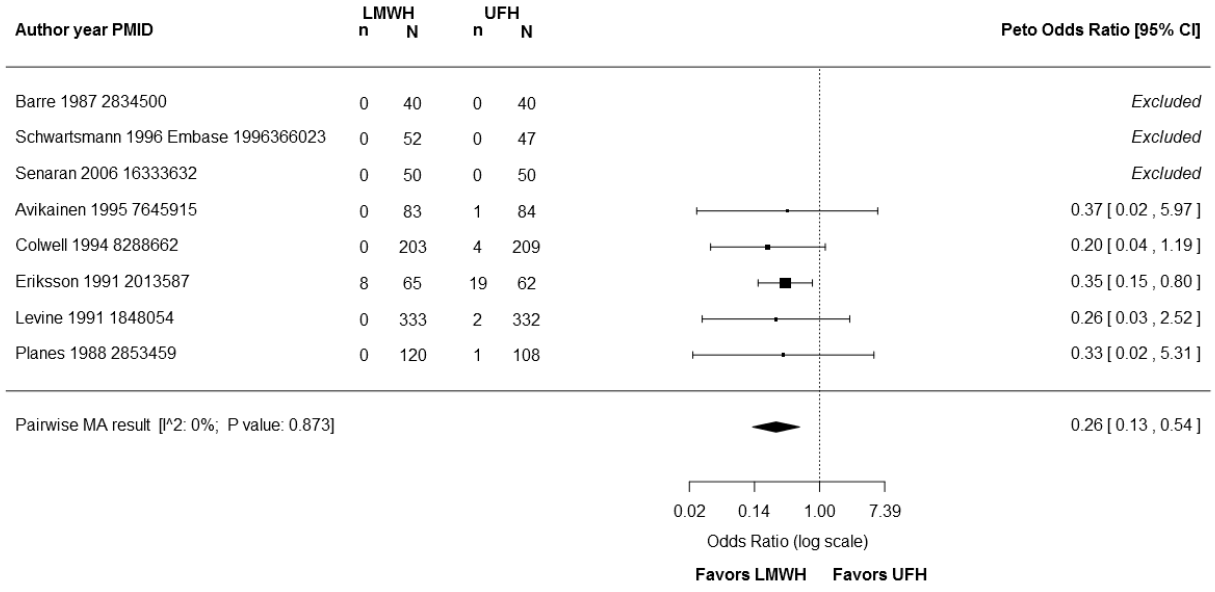
LMWH Verusus UFH

Ten RCTs (N=2387) reported on comparisons of LMWH versus UFH.[64-73] All 10 reported VTE-related outcomes.

Total PE

Eight RCTs (N=1878) that compared LMWH and UFH reported total PE (0-12.3% in LMWH, 0-30.6% in UFH).[64-66, 69-73] The rate was lower in the LMWH group in five RCTs,[64-66, 69, 73] which was statistically significant in one.[65] Three RCTs reported no occurrence of PE in either comparison group.[70-72] Meta-analysis of the remaining five RCTs yielded a summary OR of 0.26 (95% CI 0.13 to 0.54) for the risk of total PE, statistically significantly favoring LMWH. Study results were homogeneous (I^2 = 0%, P = 0.87) (**Figure 1.thr.9**).

Figure 1.thr.9. Forest plot: Total PE, LMWH vs. UFH

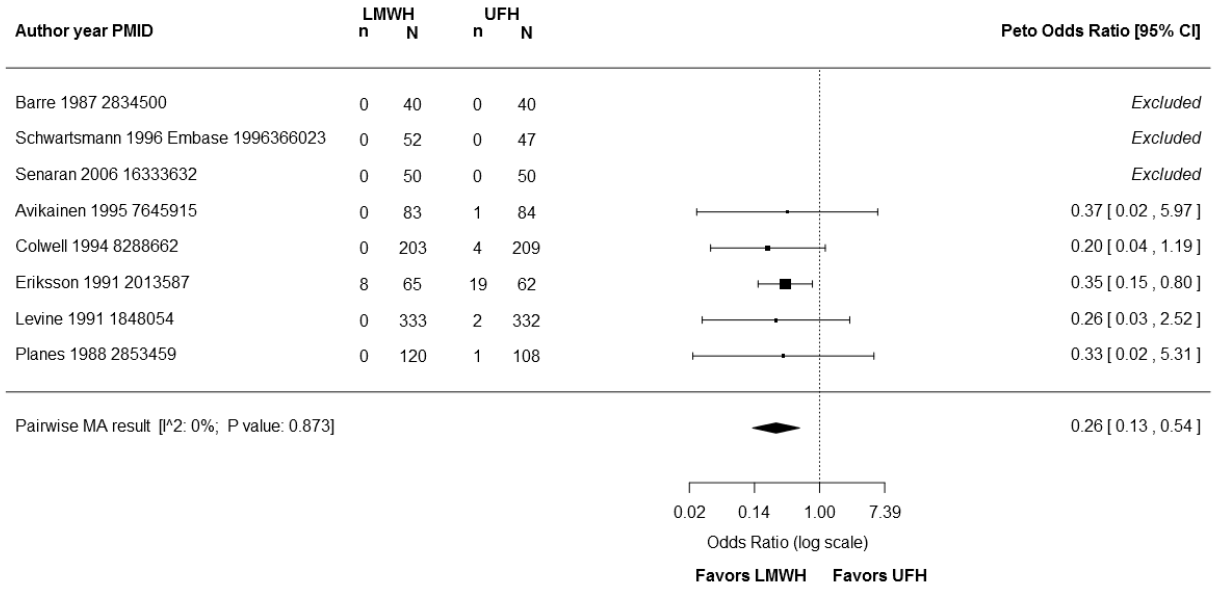


Forest plot of randomized controlled trials with calculated Peto odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with Peto fixed effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: LMWH = low molecular weight heparin, PMID = PubMed identifier, UFH = unfractionated heparin.

Total DVT

Ten RCTs (N=2219) reported total DVT in comparisons of LMWH and UFH (0-30.2% in LMWH, 4.0-42.4% in UFH).[64-73] The rate was lower in the LMWH group in seven RCTs,[64-67, 71-73] which was statistically significant in one.[66] Meta-analysis of the 10 RCTs found no significant difference between the two drug classes for the risk of total DVT (summary OR=0.84; 95% CI 0.60 to 1.18). Study results were homogeneous (I^2 = 36%, P = 0.16) (**Figure 1.thr.10**).

Figure 1.thr.10. Forest plot: Total DVT, LMWH vs. UFH

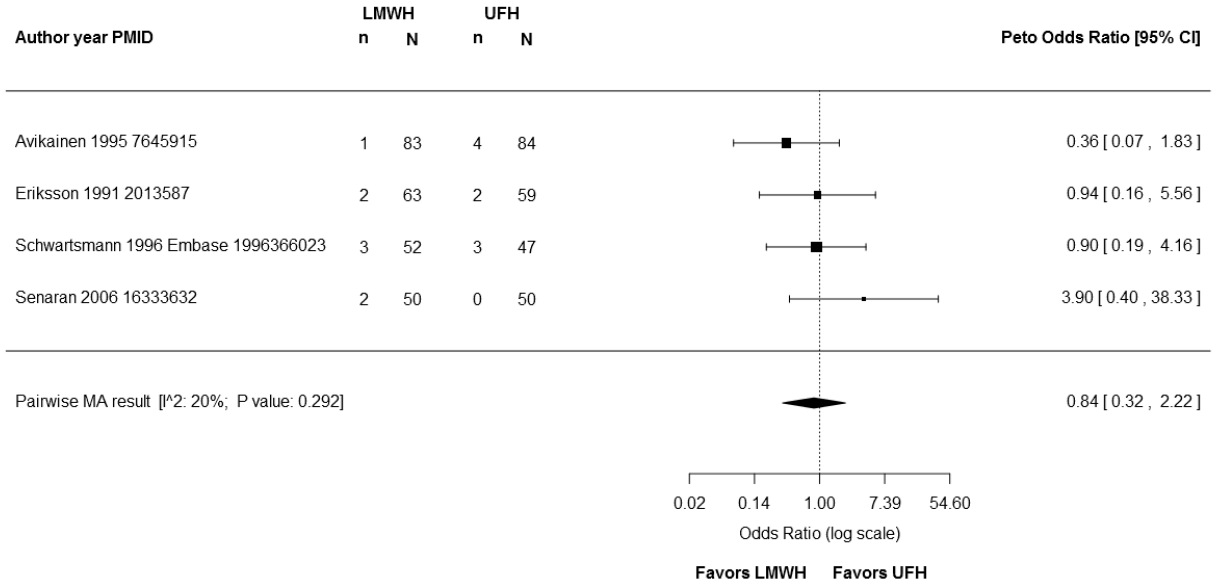


Forest plot of randomized controlled trials with calculated Peto odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with Peto fixed effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: LMWH = low molecular weight heparin, PMID = PubMed identifier, UFH = unfractionated heparin.

Symptomatic DVT

Four RCTs (N=488) reported on symptomatic DVT comparing LMWH and UFH (1.2-5.8% in LMWH, 0-6.4% in UFH).[65, 71-73] Patients who received LMWH had a lower event rate in three RCTs. Meta-analysis of the four RCTs found an imprecise estimate of OR with no significant difference for the risk of symptomatic DVT between the two comparison groups (summary OR=0.84, 95% CI 0.32 to 2.22). Study results were homogeneous (I^2 = 20%, P = 0.29) (**Figure 1.thr.11**).

Figure 1.thr.11. Forest plot: Symptomatic DVT, LMWH vs. UFH

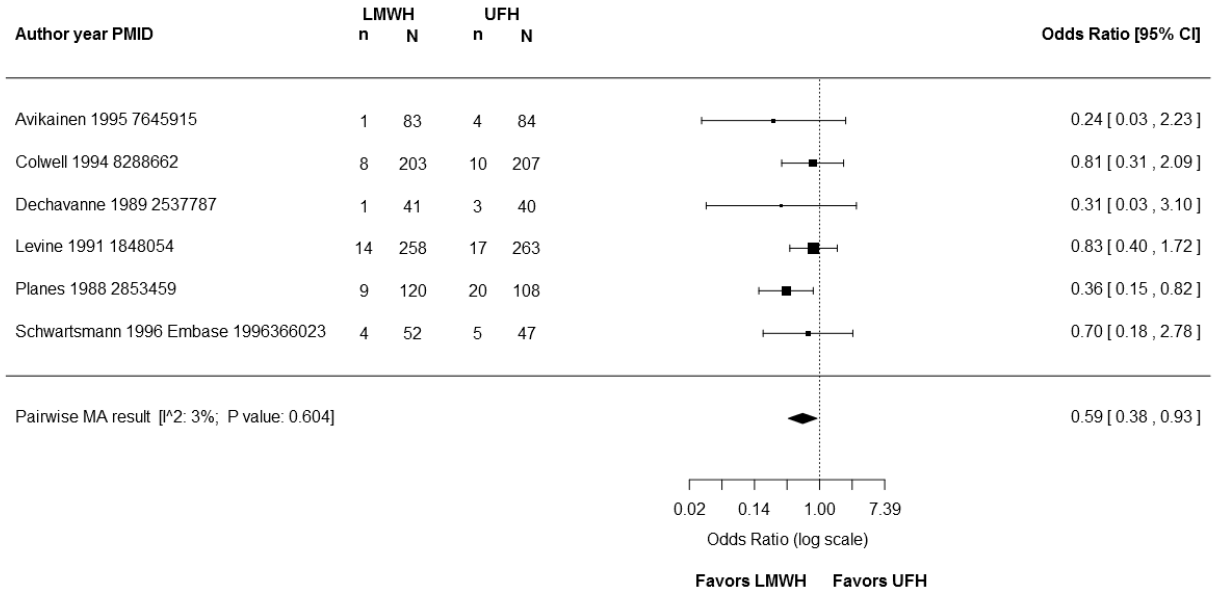


Forest plot of randomized controlled trials with calculated Peto odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with Peto fixed effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: LMWH = low molecular weight heparin, PMID = PubMed identifier, UFH = unfractionated heparin.

Proximal DVT

Six RCTs (N=1506) compared LMWH and UFH and reported proximal DVT (1.2-7.7% in LMWH, 4.8-18.5% in UFH).[64, 66, 67, 69, 72, 73] The event rate was significantly lower in the LMWH group in one RCT.[66] Meta-analysis of the six RCTs yielded a summary OR of 0.59 (95% CI 0.38 to 0.93) for the risk of proximal DVT, significantly favoring LMWH. Study results were homogeneous (I^2 = 3%, P = 0.60) (**Figure 1.thr.12**).

Figure 1.thr.12. Forest plot: Proximal DVT, LMWH vs. UFH



Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: LMWH = low molecular weight heparin, PMID = PubMed identifier, UFH = unfractionated heparin.

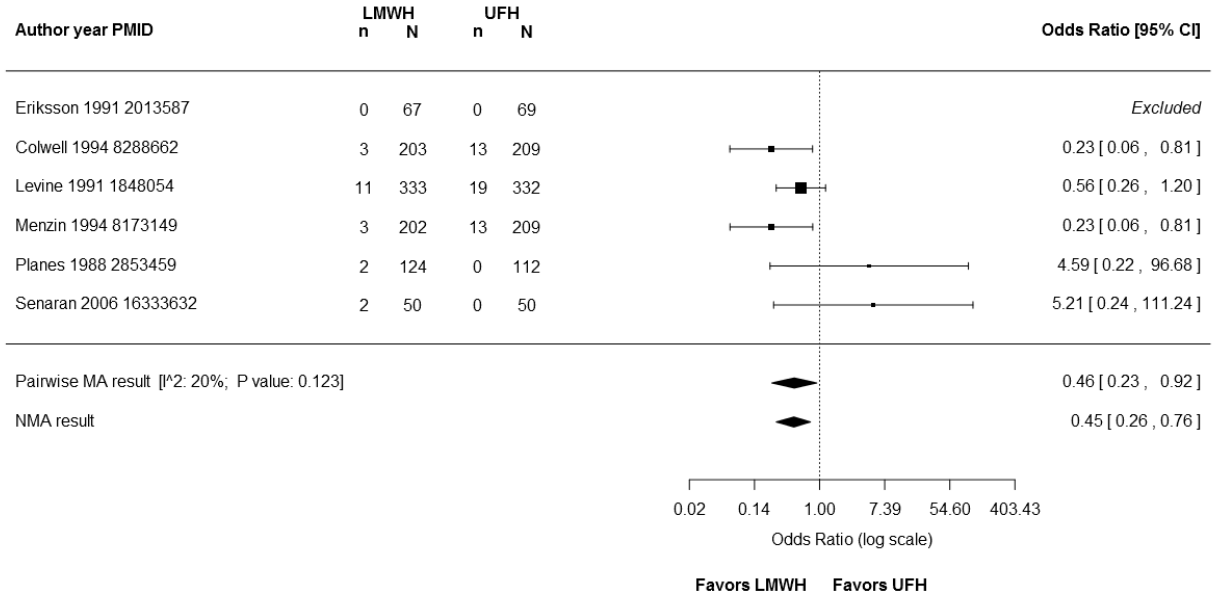
Other VTE Outcomes

One RCT found no significant difference in symptomatic VTE.[71] Seven studies reported no fatal PE events.[64-66, 69-72]

Major Bleeding

Six RCTs (N=1960) that examined LMWH and UFH reported major bleeding (0-4.0% in LMWH, 0-6.2% in UFH).[64-66, 68, 69, 71] The rate was lower in patients who received LMWH in three RCTs,[64, 68, 69] statistically significantly so in two.[68, 69] One RCT reported no major bleeding in either group. Meta-analysis of the other five RCTs yielded a summary OR of 0.46 (95% CI 0.23 to 0.92) for the risk of major bleeding, significantly favoring LMWH. Study results were homogeneous (I^2 = 20%, P = 0.12) (**Figure 1.thr.13**).

Figure 1.thr.13. Forest plot: Major bleeding LMWH vs. UFH



Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result) and equivalent summary estimate from corresponding network meta-analysis (NMA). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: LMWH = low molecular weight heparin, PMID = PubMed identifier, UFH = unfractionated heparin.

Other Bleeding Events

Six RCTs had no fatal bleeding events,[64-66, 70-72] one of which also reported no bleeding events leading to reoperation. Two studies found no significant differences in rates of surgical site bleeding. Six studies reported on 30-day mortality but four of the studies had no deaths and the remaining two found no significant differences in mortality rates.[64-66, 69, 71, 72]

Other Adverse Events

Three RCTs found no significant differences in rates of heparin-induced thrombocytopenia, but one of the studies had no events.[64, 69, 71]

Adherence

No study reported on adherence.

LMWH Versus VKA

Four RCTs (N=5332) compared LMWH and VKA.[74-77] All reported on VTE-related outcomes.

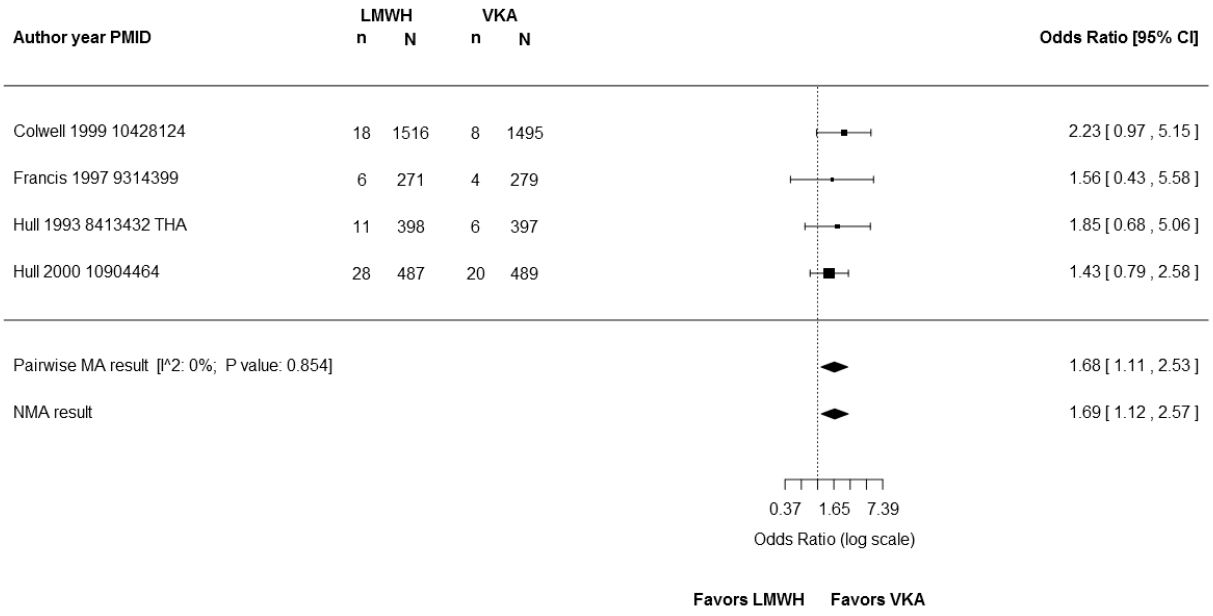
VTE Outcomes

Two RCTs found no significant difference in symptomatic VTE.[74, 75] Three RCTs found no significant differences in total PE (with no events in one study) and in fatal PE (with no events in two studies).[74-76] The three studies found no significant differences in total DVTs, two of which also found no significant differences in symptomatic DVTs.[74-76] However, one of the three studies found significantly fewer proximal DVTs with LMWH than VKA, but the three studies were not consistent (range of ORs: 0.27 [95% CI 0.07 to 0.98] to 1.27 [95% CI 0.60 to 2.69]).

Major Bleeding

Four RCTs (N=5332) reported major bleeding which assessed LMWH and VKA (1.2-5.8% in LMWH, 0.5-4.1% in VKA).[74-77] The rate was lower in the VKA group in all the RCTs. Meta-analysis of the four RCTs showed a significantly lower risk of major bleeding in the VKA group (summary OR=1.68, 95% CI 1.11 to 2.53). Study results were homogeneous (I^2 = 0%, P = 0.85) (**Figure 1.thr.14**).

Figure 1.thr.14. Forest plot: Major bleeding LMWH vs. VKA



Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result) and equivalent summary estimate from corresponding network meta-analysis (NMA). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: LMWH = low molecular weight heparin, PMID = PubMed identifier, VKA = vitamin K antagonist.

Other Bleeding

Two RCTs reported no fatal bleeding events.[75, 76] One study found no significant difference in bleeding events leading to reoperation.[77] Two of three studies found significant differences in surgical site bleeding, with all three studies favoring VKA (range of ORs: 1.63 [95% CI 0.88 to

3.03] to 4.26 [95% CI 1.19 to 15.3]).[74, 76, 77] One study reported no 30-day mortality events and one study reported no incidents of heparin-induced thrombocytopenia.[76]

Adherence

No study reported on adherence.

Mechanical Device Versus UFH

One RCT (N=132) compared a mechanical device and UFH.[78] The study found significantly fewer total DVTs with the mechanical device, no fatal bleeding events, and no significant difference in 30-day mortality.

Mechanical Device Versus VKA

Three RCTs (N=434) compared a mechanical device with VKA.[79-81] One study reported no PE events in either arm. A U.S.-based registry NRCS of 14,657 THR patients found no significant difference in total PE between mechanical devices and LMWH (OR 1.34, 95% CI 0.51 to 3.53), controlling for age, sex, anesthesia risk category, and use of general anesthesia (**Appendix Table F4**).[23] One of three RCTs found a statistically significant difference in total DVTs favoring mechanical device, but the other two RCTs found no significant difference; the range of OR estimates was 0.18 (95% CI 0.05 to 0.67) to 1.00 (95% CI 0.41 to 2.45). However, the same three RCTs consistently found more proximal DVTs mechanical devices than VKA, but again only one study was statistically significant; the range of OR estimates was 2.39 (95% CI 0.77 to 7.41) to 4.69 (95% CI 0.22 to 100.4).

No bleeding events were found for major bleeding (1 RCT), fatal bleeding (2 RCTs), or bleeding leading to reoperation (1 RCT). Two RCTs reported on 30-day mortality; one had no deaths and one found no significant difference between intervention classes.

Table X1. Results summary: Total hip replacement, intervention class vs. class comparisons

Comparison	Outcome	Studies, N	OR, 1 *(Summary OR)*	OR, 2	OR, 3	No Events*
Antiplatelet vs. VKA	DVT, Total	1	0.71 (0.34, 1.47)			
	DVT, Proximal	1	0.31 (0.08, 1.18)			
Antiplatelet vs. VKA (+mechanical both arms)	PE, Total	1	3.00 (0.12, 74.9)			
	DVT, Proximal	1	1.13 (0.36, 3.55)			
DTI vs. FXaI (+LMWH both arms)	DVT, Total	1	0.54 (0.12, 2.42)			
DTI vs. UFH	PE, Total	2	0.11 (0.01, 2.03)	3.42 (0.14, 84.4)		
	PE, Fatal	2	No estimate			2 RCTs
	DVT, Total	2	**0.26 (0.13, 0.50)**	**0.44 (0.28, 0.69)**		
	DVT, Proximal	2	**0.13 (0.05, 0.31)**	**0.18 (0.05, 0.62)**		
	Bleeding, Fatal	2				2 RCTs
	Bleeding, Leading to reoperation	2	2.01 (0.37, 11.1)			1 RCT
	Bleeding, Surgical site/joint	1	1.15 (0.41, 3.21)			
	Mortality, 30 day or in-hospital	2	0.20 (0.01, 4.15)	0.38 (0.02, 9.28)		
FEI vs. FXaI	VTE, Total	1	1.11 (0.44, 2.78)			
	VTE, Symptomatic	1	No estimate			1 RCT
	PE, Fatal	1	No estimate			1 RCT
	PE, Symptomatic	1	No estimate			1 RCT
	DVT, Total	1	1.11 (0.44, 2.78)			
	DVT, Symptomatic	1	No estimate			1 RCT
	DVT, Proximal	1	4.02 (0.45, 36.3)			
	Bleeding, Major	1	11.22 (0.62, 204)			
	Bleeding, Surgical site/joint	1	**2.87 (1.30, 6.34)**			
	Mortality, 30 day or in-hospital	1	0.33 (0.01, 8.15)			
LMWH vs. DTI	VTE, Symptomatic	1	6.09 (0.73, 50.6)			
	PE, Total	2	0.60 (0.14, 2.50)	2.40 (0.62, 9.30)		
	PE, Fatal	2	0.34 (0.01, 8.36)			1 RCT
	DVT, Total	3	1.14 (0.79, 1.64)	1.18 (0.67, 2.07)	**1.52 (1.19, 1.94)**	
	DVT, Symptomatic	2	0.17 (0.02, 1.37)	9.12 (0.49, 170)		
	DVT, Proximal	3	1.35 (0.53, 3.42)	**1.73 (1.13, 2.65)**	**1.89 (1.04, 3.44)**	
	Bleeding, Major	*4 (MA)*	*0.79 (0.55, 1.14)*			
	Bleeding, Fatal	2	0.33 (0.01, 8.13)			1 RCT
	Bleeding, Leading to reoperation	1	1.49 (0.25, 8.94)			
	Bleeding, Surgical site/joint	1	1.03 (0.86, 1.24)			

Comparison	Outcome	Studies, N	OR, 1 *(Summary OR)*	OR, 2	OR, 3	No Events*
	Mortality, 30 day or in-hospital	3	0.14 (0.01, 2.75)	0.25 (0.03, 2.28)	3.03 (0.12, 74.5)	
LMWH vs. FXaI	*VTE, Total*	*7 (MA)*	***1.82 (1.23, 2.71)***			
	VTE, Symptomatic	*6 (MA)*	***0.52 (0.31, 0.87)***			2 RCTs
	PE, Total	4	0.33 (0.11, 1.03)	1.01 (0.14, 7.15)	1.67 (0.40, 7.01)	1 RCT
	PE, Fatal	8	0.33 (0.01, 8.21)	2.00 (0.18, 22.1)		6 RCTs
	PE, Symptomatic	5	0.56 (0.02, 13.8)			4 RCTs
	DVT, Total	*9 (MA)*	***1.97 (1.42, 2.74)***			
	DVT, Symptomatic	*8 (MA)*	*0.82 (0.34, 1.97)*			
	DVT, Proximal	*10 (MA)*	***2.40 (1.23, 4.69)***			2 RCTs
	Bleeding, Major	*9 (MA)*	***0.72 (0.52, 0.99)***			2 RCTs
	Bleeding, Fatal	*3*	No estimate			3 RCTs
	Bleeding, Leading to reoperation	3	0.60 (0.14, 2.53)	1.00 (0.14, 7.11)	1.01 (0.06, 16.1)	
	Bleeding, Surgical site/joint	3	0.50 (0.05, 5.56)	0.72 (0.44, 1.17)	0.89 (0.45, 1.75)	
	Mortality, 30 day or in-hospital	3	0.50 (0.12, 2.00)	2.02 (0.37, 11.0)		1 RCT
	Adverse event, Serious	*5 (MA)*	*0.95 (0.78, 1.17)*			
	Adherent/Compliant	2	0.11 (0.01, 2.05)	**2.64 (1.35, 5.14)**		
LMWH vs. Mechanical	VTE, Total	1	1.03 (0.42, 2.54)			
	PE, Total	1	0.33 (0.01, 8.08)			
	PE, Fatal	2	No estimate			2 RCTs
	PE, Symptomatic	1	1.03 (0.14, 7.40)			
	DVT, Total	3	0.70 (0.36, 1.36)	1.00 (0.06, 17.0)	1.03 (0.38, 2.81)	
	DVT, Symptomatic	2	2.98 (0.12, 73.8)			1 RCT
	DVT, Proximal	3	0.67 (0.31, 1.45)	0.68 (0.11, 4.14)	1.00 (0.06, 16.9)	
	Bleeding, Major	1	**24.9 (1.46, 425)**			
	Bleeding, Fatal	1	No estimate			1 RCT
	Mortality, 30 day or in-hospital	1	No estimate			1 RCT
	Adverse event, Serious	1	3.53 (0.96, 13.0)			
LMWH vs. UFH	VTE, Symptomatic	1	1.00 (0.14, 7.39)			
	PE, Total	*8 (MA)*	***0.26 (0.13, 0.54)***			3 RCTs
	PE, Fatal	7	No estimate			7 RCTs
	DVT, Total	*10 (MA)*	*0.84 (0.60, 1.18)*			
	DVT, Symptomatic	*4 (MA)*	*0.84 (0.32, 2.22)*			
	DVT, Proximal	*6 (MA)*	***0.59 (0.38, 0.93)***			
	Bleeding, Major	*6 (MA)*	***0.46 (0.23, 0.92)***			1 RCT
	Bleeding, Fatal	6	No estimate			6 RCTs
	Bleeding, Leading to reoperation	1	No estimate			1 RCT

Comparison	Outcome	Studies, N	OR, 1 *(Summary OR)*	OR, 2	OR, 3	No Events*
	Bleeding, Surgical site/joint	2	0.14 (0.02, 1.17)	0.73 (0.16, 3.46)		
	Mortality, 30 day or in-hospital	6	0.20 (0.01, 4.27)	0.34 (0.01, 8.45)		4 RCTs
	Heparin-induced thrombocytopenia	3	0.05 (<0.01, 0.88)	0.34 (0.01, 8.43)		1 RCT
LMWH vs. VKA	VTE, Symptomatic	2	0.97 (0.66, 1.41)	3.02 (0.61, 15.1)		
	PE, Total	3	1.24 (0.58, 2.65)	3.00 (0.12, 73.9)		1 RCT
	PE, Fatal	3	2.96 (0.12, 72.7)			2 RCTs
	DVT, Total	3	**0.48 (0.32, 0.72)**	**0.49 (0.29, 0.82)**	0.87 (0.60, 1.25)	
	DVT, Symptomatic	2	0.66 (0.29, 1.49)	1.03 (0.69, 1.55)		
	DVT, Proximal	3	**0.27 (0.07, 0.98)**	0.60 (0.26, 1.35)	1.27 (0.60, 2.69)	
	Bleeding, Major	*4 (MA)*	***1.68 (1.11, 2.53)***			
	Bleeding, Fatal	2	No estimate			2 RCTs
	Bleeding, Leading to reoperation	1	3.10 (0.13, 76.4)			
	Bleeding, Surgical site/joint	3	1.63 (0.88, 3.03)	**2.78 (1.00, 7.73)**	**4.26 (1.19, 15.3)**	
	Mortality, 30 day or in-hospital	1	No estimate			1 RCT
	Heparin-induced thrombocytopenia	1	No estimate			1 RCT
Mechanical vs. UFH	DVT, Total	1	**0.28 (0.12, 0.67)**			
	Bleeding, Fatal	1	No estimate			1 RCT
	Mortality, 30 day or in-hospital	1	0.32 (0.01, 7.96)			
	PE, Total	1	No estimate			1 RCT
	DVT, Total	3	**0.18 (0.05, 0.67)**	0.80 (0.43, 1.48)	1.00 (0.41, 2.45)	
	DVT, Proximal	3	2.39 (0.77, 7.41)	**4.65 (1.27, 17.0)**	4.69 (0.22, 100)	
	Bleeding, Major	1	No estimate			1 RCT
	Bleeding, Fatal	2	No estimate			2 RCTs
	Bleeding, Leading to reoperation	1	No estimate			1 RCT
	Mortality, 30 day or in-hospital	2	1.05 (0.06, 17.1)			1 RCT

All outcomes for all pairwise comparisons with data from at least one study. If 3 or fewer randomized controlled trials (RCT) with analyzable data (i.e., at least 1 event per study) then each study's odds ratio (OR) is listed in ascending order from left to right. If there were ≥4 analyzable studies, then meta-analysis was conducted and summary OR is reported. These are indicated by italics and by MA (meta-analysis) in the study number column. Statistically significant OR estimates are in bold text. The corresponding studies for each analysis can be found in Appendix F.

Other abbreviations: DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venothromboembolism, Antiplatelet = antiplatelet agent, VKA = vitamin K antagonist, Mechanical = mechanical devices, DTI = direct thrombin inhibitor, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, FEI = factor VIII inhibitor, UFH = unfractionated heparin.

* Number of RCTs with no events in both arms.

Cross-Study Subgroup Analyses

As noted at the start of the Results section, studies were generally homogeneous in terms of patient eligibility criteria, such that most studies included all-comers without eligibility restrictions based on demographics, or other major patient or surgery subtypes. While some studies were restricted based on past bleeding history or chronic antiplatelet or VKA use, no RCTs were restricted to the converse populations (only patients with bleeding history or on antithromobotic medication). Thus, across-study comparisons of subgroup factors are limited.

Among THR RCTs, differences between studies based on industry funding was analyzable for only the comparison of LMWH versus UFH. For total DVT, by random effects model metaregresion no significant difference (P=0.51) was found between the eight industry-funded studies (summary OR 0.91, 95% CI 0.59 to 1.41) and the two studies without reported industry support (summary OR 0.71, 95% CI 0.38 to 1.32). Similarly, for major bleeding, no significant difference (P=0.95) was found between the four industry-funded studies (summary OR 0.62, 95% CI 0.13 to 2.93) and the two studies without industry support (summary OR 0.56, 95% CI 0.26 to 1.20).

For the comparison of Asian versus non-Asian RCTs, only the comparison of LMWH versus FXaI was analyzable. For total DVT, no significant difference (P=0.56) was found between the five Asian studies (summary OR 1.63, 95% CI 0.81 to 3.31) and the four non-Asian studies (summary OR 2.08, 95% CI 1.40 to 3.09) by random effects model metaregresion. The non-Asian studies included more patients, largely explaining the difference in statistical significance between the two sets of studies. Overall, the same percentage of Asian and non-Asian study participants had a DVT among these RCTs (4.7%). Similarly, for major bleeding, no significant difference (P=0.16) was found between the four Asian RCTs with major bleeding events (summary OR 1.95, 95% CI 0.46 to 8.22) and the five non-Asian studies (OR 0.68, 95% CI 0.49 to 0.94). Again, the non-Asian studies included more patients, largely explaining the difference in statistical significance between the two sets of studies. The Asian RCTs had relatively few events, with an overall major bleeding rate of 0.7 percent compared to 1.5 percent among all non-Asian RCTs (P=0.041); however, if the European study with an atypically high reported major bleeding rate (3.5%) is excluded, the non-Asian RCTs have a major bleeding rate of 0.9 percent, similar to the reported Asian rate (P=0.59).

Total Knee Replacement

The results summary table (**Table X2**) is presented at the end of the TKR section. It includes results for all reported comparisons and outcomes from TKR RCTs. The reader should refer to this table for each results section summary even though the table is not repeatedly cited in each section. Where data are summarized only appendix tables or are summarized in figures, these are cited.

Antiplatelet Drug Versus FXaI

One RCT (N=212) compared an antiplatelet drug versus an FXaI.[82] The study had no PE events, but found significantly fewer total DVT in the FXaI group and no significant difference in symptomatic DVT.

The study found no significant difference in wound complications between the two groups. The study did not report on adherence.

Antiplatelet Drug Versus Mechanical Devices

One RCT (N=119) compared an antiplatelet drug versus a mechanical device.[83]The study reported a significantly fewer total DVT in patients who received mechanical prophylaxis, but no significant difference in proximal DVT between the two classes. The study did not report adverse events or adherence data.

A U.S.-based registry NRCS of 25,388 TKR patients found no significant difference in total PE between aspirin and mechanical devices (OR 0.63, 95% CI 0.32 to 1.26), controlling for age, sex, anesthesia risk category, and use of general anesthesia (**Appendix Table F4**).[30]

Subgroup Analysis

The RCT compared subgroups of patients who received unilateral or bilateral TKR surgery. They found that in the unilateral group (n=72) the percent of patients with a DVT was lower for those receiving mechanical prophylaxis through a compression boot (22%) compared to those receiving aspirin (47%, P<0.03). In the bilateral group (n=47), DVT incidence was also lower in patients who used compression boots (48%) compared with those who received aspirin (68%), but this difference was not significant (P<0.20).[83] Whether the treatment effect differed between unilateral and bilateral subgroups was not analyzed.

Antiplatelet Drug Versus VKA

One RCT (N=189) comparing an antiplatelet drug versus a VKA found no significant difference in either total DVT or proximal DVT between the two classes.[37] The study did not report adverse events or adherence data.

DTI Versus FXaI

One RCT (N=80) compared DTI versus FXaI.[84]The study reported no total PE, no total DVT, and no major bleeding in either group. The study did not report adherence data.

LMWH Versus Antiplatelet Drug

One RCT (N=222) compared LMWH versus an antiplatelet drug.[82] The study reported no total PE in either group. It found no significant difference in total DVT and symptomatic DVT between the intervention classes. The study also found no significant difference in wound complications. The study did not report adherence data.

LMWH Versus DTI

Five RCTs (N=3514) compared LMWH versus DTI.[46, 84-87] All reported on VTE-related outcomes.

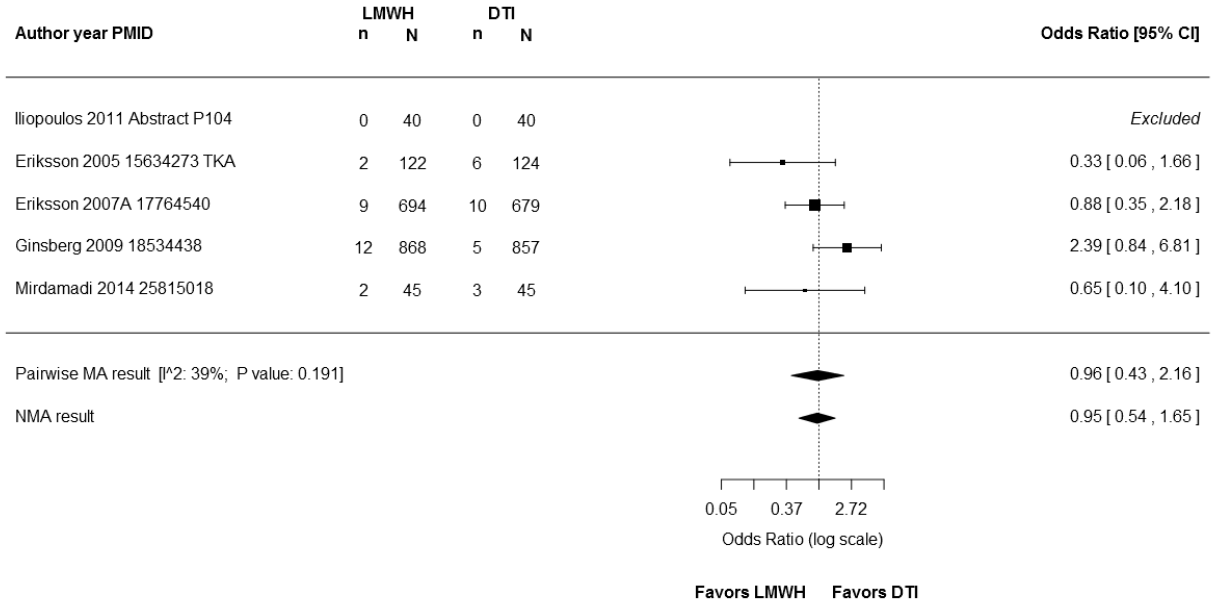
VTE Outcomes

Two RCTs reported total PE;[84, 85] one had no PE events and the other found no significant difference between the two comparison groups. One study found no significant difference in fatal PE between arms, and one reported no fatal PE in either arm.[85, 87] Two studies reported total DVT;[46, 84] one had no DVT events but the other found significantly fewer total DVTs in the DTI group. Three RCTs found no significant differences in symptomatic DVT between the two drug classes with inconsistent estimates across studies, but one near-significant OR favoring DTI (range of ORs: 0.67 [95% CI 0.21 to 2.12] to 7.96 [95% CI 0.99 to 63.9]).[85-87] Two RCTs found no significant difference in proximal DVT between arms.[46, 86]

Major Bleeding

Five RCTs (N=3514) that compared LMWH and DTI reported major bleeding (0-4.4% in LMWH, 0-6.7% in DIT).[46, 84-87] The rate was lower in the LMWH group in three RCTs.[46, 85, 87] One RCT reported no occurrence of major bleeding in either of the groups. Meta-analysis of the other four RCTs found an imprecise estimate of OR with no significant difference between the two drug classes for the risk of major bleeding (summary OR=0.96; 95% CI 0.43 to 2.16). Study results were homogeneous (I^2 = 39%, P = 0.19) (**Figure 1.tkr.1**).

Figure 1.tkr.1. Forest plot: Major bleeding, LMWH vs. DTI



Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result) and equivalent summary estimate from corresponding network meta-analysis (NMA). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: DTI = direct thrombin inhibitor, LMWH = low molecular weight heparin, PMID = PubMed identifier.

Other Adverse Events

Two RCTs reported no fatal bleeding.[85, 86] One study found no significant difference in bleeding leading to reoperation between the two classes.[85] One study reported significantly lower rate of bleeding at surgical site or joint in the DTI group.[86] One study found no significant difference in 30-day mortality.[85]

Adherence

No studies reported adherence data.

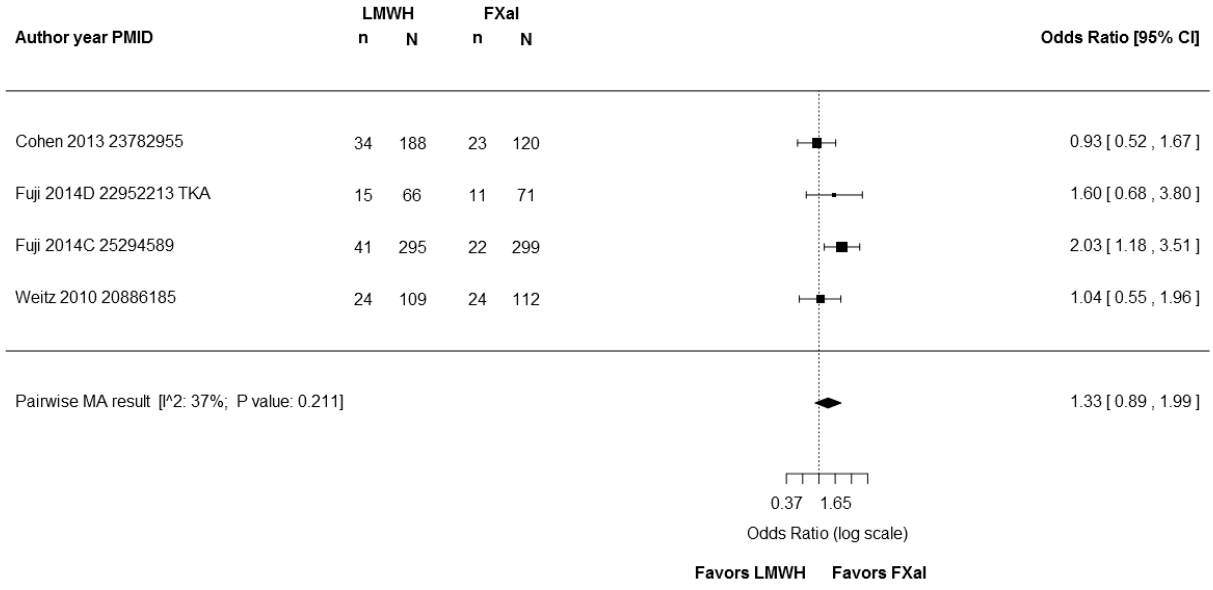
LMWH Versus FXaI

Ten RCTs (N=6350) compared LMWH versus FXaI.[49, 82, 84, 88-94] All 10 reported VTE-related outcomes.

Total VTE

Four RCTs[49, 92-94] (N=1260) reported the outcome of total VTE for the comparison of LMWH and FXaI (13.9-22.7% in LMWH, 7.4-21.4% in FXaI). Three RCTs[49, 92, 93] had a lower event rate in the FXaI group, which was statistically significant in one.[92] No significant difference was shown for the risk of total VTE between the two drug classes in the meta-analysis of the four RCTs (summary OR=1.33, 95% CI 0.89 to 1.99). Study results were homogeneous (I^2 = 37%, P = 0.21) (**Figure 1.tkr.2**).

Figure 1.tkr.2. Forest plot: Total VTE, LMWH vs. FXaI

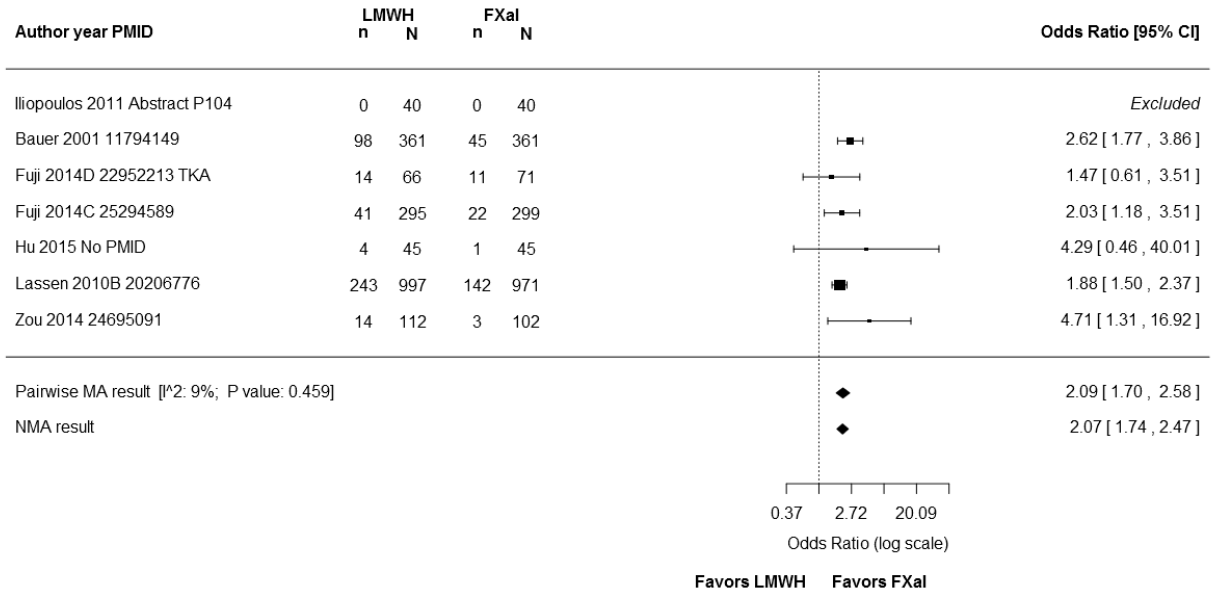


Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, PMID = PubMed identifier.

Total DVT

Seven RCTs (N=3805) reported total DVT for comparisons of LMWH and FXaI (0-27.2% in LMWH, 0-15.5% in FXaI).[49, 82, 84, 89-92] The DVT rate was lower in the FXaI group in six RCTs,[49, 82, 89-92] statistically significantly so in four.[82, 90-92] One RCT reported no occurrence of DVT events in either comparison group.[84] Meta-analysis of the other six RCTs yielded a summary OR of 2.09 (95% CI 1.70 to 2.58) for the risk of total DVT, significantly favoring FXaI. Study results were homogeneous (I^2 = 9%, P = 0.46) (**Figure 1.tkr.3**).

Figure 1.tkr.3. Forest plot: Total DVT, LMWH vs. FXaI

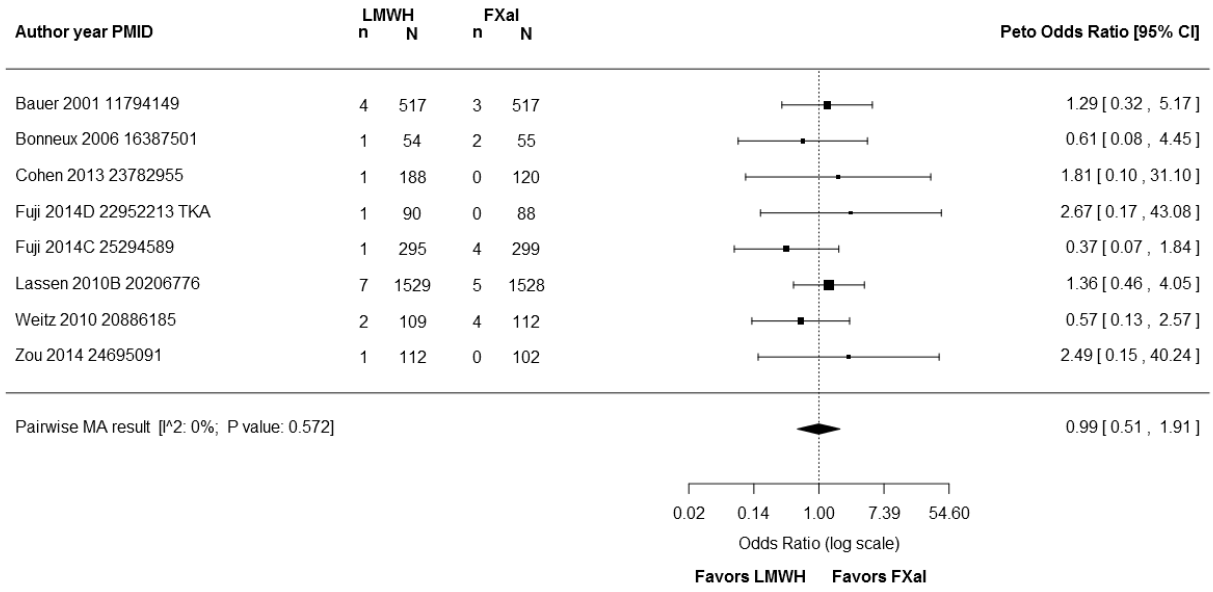


Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result) and equivalent summary estimate from corresponding network meta-analysis (NMA). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, PMID = PubMed identifier.

Symptomatic DVT

Eight RCTs (N=5715) comparing LMWH and FXaI reported symptomatic DVT (0.3-1.9% in LMWH, 0-3.6% in FXaI).[49, 82, 88, 90-94] The DVT rate was somewhat lower in the FXaI group in five RCTs.[49, 82, 90, 91, 94] Meta-analysis of the eight RCTs showed no significant difference between the two drug classes for the risk of symptomatic DVT (summary OR=0.99; 95% CI 0.51 to 1.91). Study results were homogeneous (I^2 = 0%, P = 0.57) (**Figure 1.tkr.4**).

Figure 1.tkr.4. Forest plot: Symptomatic DVT, LMWH vs. FXaI

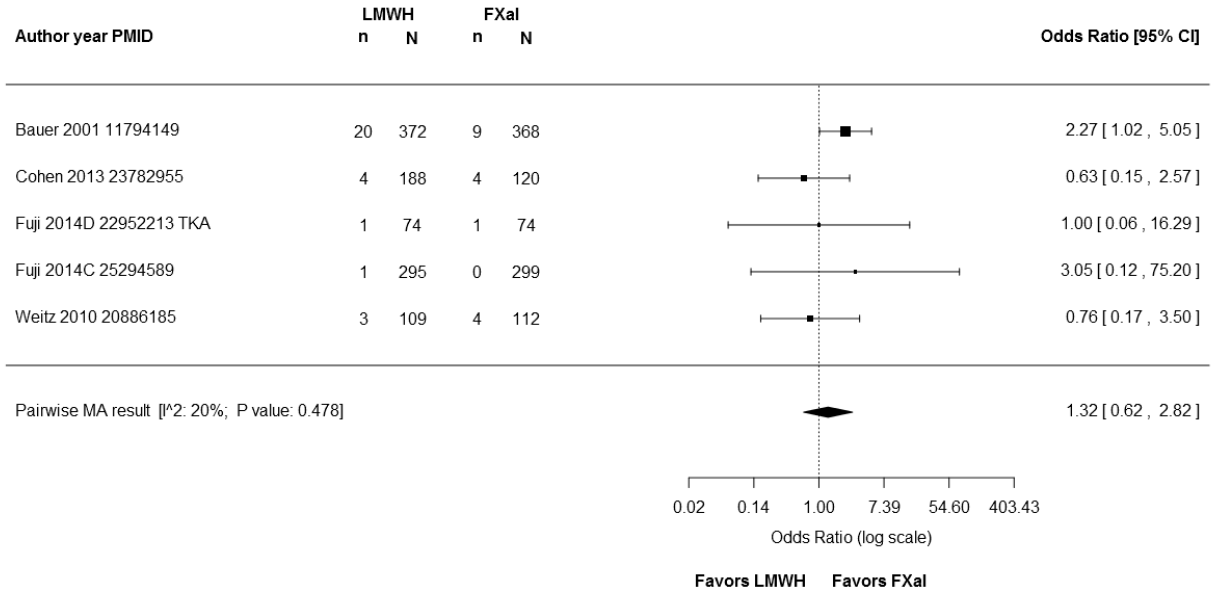


Forest plot of randomized controlled trials with calculated Peto odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with Peto fixed effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, PMID = PubMed identifier.

Proximal DVT

Five RCTs (N=2011) reported proximal DVT for the comparison of LMWH and FXaI (0.3-5.4% in LMWH, 0-3.6% in FXaI).[49, 91-94] The rate was lower in the FXaI group in two RCTs;[91, 92] statistically significant in one.[91] The difference for the risk of proximal DVT was not significantly different between the two groups in the meta-analysis of the five RCTs (summary OR=1.32, 95% CI 0.62 to 2.82). Study results were homogeneous (I^2 = 20%, P = 0.48) (**Figure 1.tkr.5**).

Figure 1.tkr.5. Forest plot: Proximal DVT, LMWH vs. FXaI



Forest plot of randomized controlled trials with calculated Peto odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with Peto fixed effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, PMID = PubMed identifier.

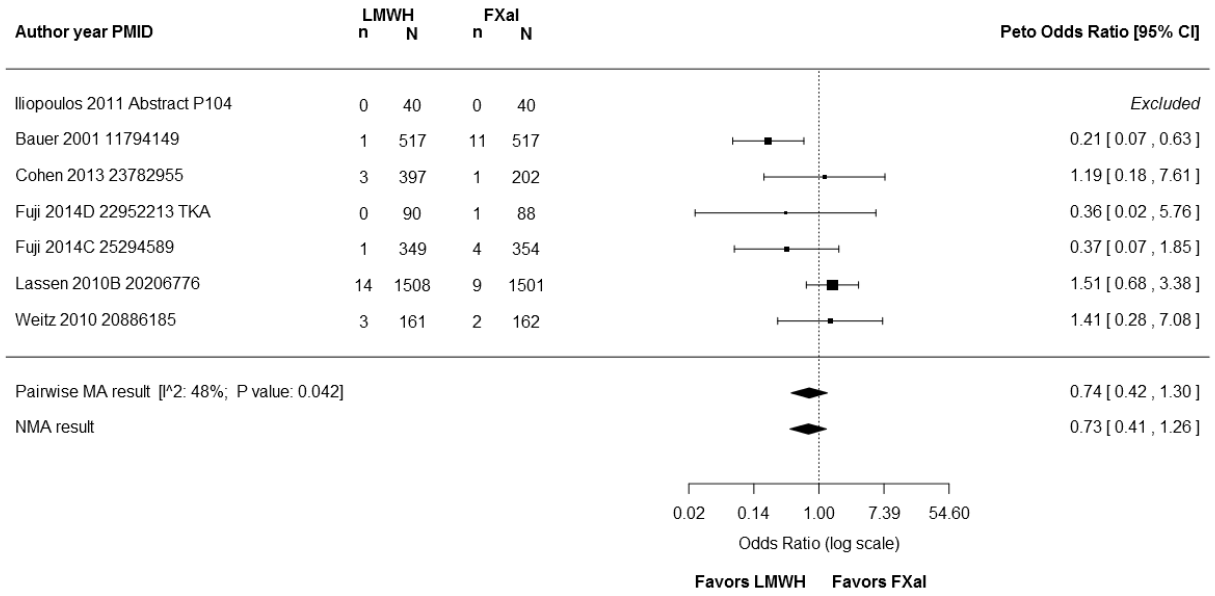
Other VTE Outcomes

Three RCTs found no significant difference in symptomatic VTE between the two classes (range of ORs: 0.25 [95% CI 0.03 to 2.26] to 2.02 [95% CI 0.69 to 5.95]).[91-93] Five RCTs reported total PE, but two had no PE events; the remaining three found no significant difference (range of ORs: 0.14 [95% CI 0.02 to 1.16] to 2.59 [95% CI 0.29 to 23.4]).[82, 84, 90, 91, 94] Five RCTs reported fatal PE, but three had no fatal PE events; the two remaining found no significant difference.[90-94] Three RCTs reported on symptomatic PE, one with no symptomatic PE events; two found no significant difference in symptomatic PE between arms.[49, 92, 93]

Major Bleeding

Seven RCTs (N=5926) evaluating LMWH and FXaI reported major bleeding (0-1.9% in LMWH, 0-2.1% in FXaI).[49, 84, 90-94] The rate was lower in the LMWH group in three RCTs,[49, 91, 92] which was statistically significant in one.[91] No major bleeding occurred in either of the groups in one RCT.[84] Meta-analysis of the remaining six RCTs found no significant difference between the two classes for the risk of major bleeding (summary OR=0.74; 95% CI 0.42 to 1.30). There was significant heterogeneity across the RCTs (I^2 = 48%, P = 0.042) (**Figure 1.tkr.6**). No clear explanation of the statistical heterogeneity could be found; however, specific drugs, doses, and regimens varied across RCTs.

Figure 1.tkr.6. Forest plot: Major bleeding, LMWH vs. FXaI



Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result) and equivalent summary estimate from corresponding network meta-analysis (NMA). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, PMID = PubMed identifier.

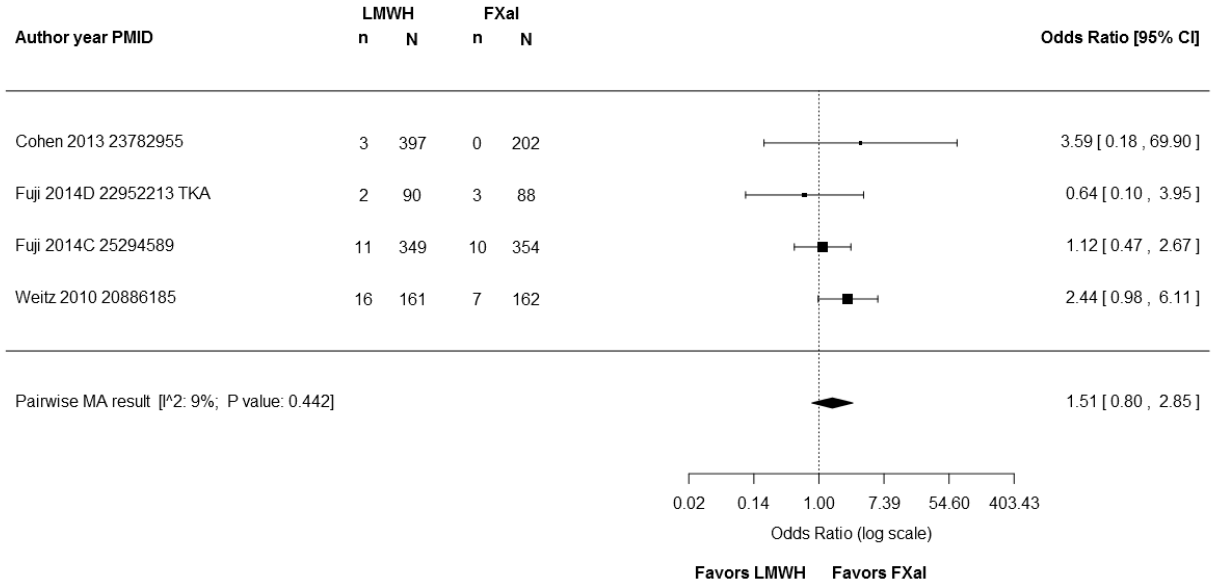
Other Bleeding Events

One RCT reported no fatal bleeding, and found no significant difference in bleeding leading to reoperation between the two classes.[91] Two RCTs found no significant difference in bleeding at surgical site or joint.[90, 92]

Serious Adverse Events

Four RCTs (N=1803) reported serious adverse events comparing LMWH (0.8-9.9%) versus FXaI (0-4.3%).[49, 92-94] Three studies reported a lower rate in the FXaI group.[92-94] Meta-analysis of the four studies yielded no significant difference for the risk of serious adverse events between the two drug classes (summary OR=1.51, 95% CI 0.80 to 2.85). Study results were homogeneous (I^2 = 9%, P = 0.44) (**Figure 1.tkr.7**).

Figure 1.tkr.7. Forest plot: Serious adverse events, LMWH vs. FXaI



Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, PMID = PubMed identifier.

Other Adverse Events

Three RCTs provided data of 30-day mortality, but one had no deaths; two found no significant difference between intervention classes.[49, 90, 91] One study reported no significant difference in wound complications.[82] One study found no significant difference in readmission due to bleeding or infection.[88]

Adherence

Two RCTs reported adherence for the comparison of LMWH and FXaI (**Appendix Table F2**). Adherence was defined as taking over 80 percent of the drugs as prescribed in one RCT.[58] The rate of adherence in this RCT was 99 percent (2595/2626) in the FXaI group, and 100 percent (2647/2659) in the LMWH group at 34 days of followup. The other RCT[50] did not define adherence, but reported 100 percent adherence (85/85 in the 15 mg group and 89/89 in the 30 mg group) in the FXaI group and 95 percent (83/87) in the LMWH group during followup for 11 to 14 days.

LMWH Versus FXIi

One RCT (N=216) compared LMWH versus FXIi.[95] The study found no significant difference between the two classes in total VTE, symptomatic VTE, total DVT, symptomatic DVT, and proximal DVT. The study had no occurrences of fatal PE or symptomatic PE.

The study had no major bleeding events. It found no difference in serious adverse events between intervention classes. The study did not report adherence data.

LMWH Versus Mechanical devices

One RCT (N=229) compared LMWH versus a mechanical device.[96] The study found no significant difference in fatal PE, total DVT, and proximal DVT. There were no fatal bleeding events and 30-day mortality was not significantly different between interventions. No adherence data were reported.

A U.S.-based registry NRCS of 25,388 TKR patients found no significant difference in total PE between LMWH and mechanical devices (OR 0.72, 95% CI 0.42 to 1.23), controlling for age, sex, anesthesia risk category, and use of general anesthesia (**Appendix Table F4**).[30]

LMWH Versus UFH

Two RCTs (N=638) compared LMWH versus UFH.[97, 98]Both reported on total PE, but one had no PE events; the other study found no significant difference between classes. This latter study also found no significant difference in fatal PE. Both studies found no significant difference in total DVT and proximal DVT. One study also reported no significant difference in symptomatic DVT.

One study found no significant difference between the two classes in major bleeding and bleeding at surgical site or joint. No adherence data were reported.

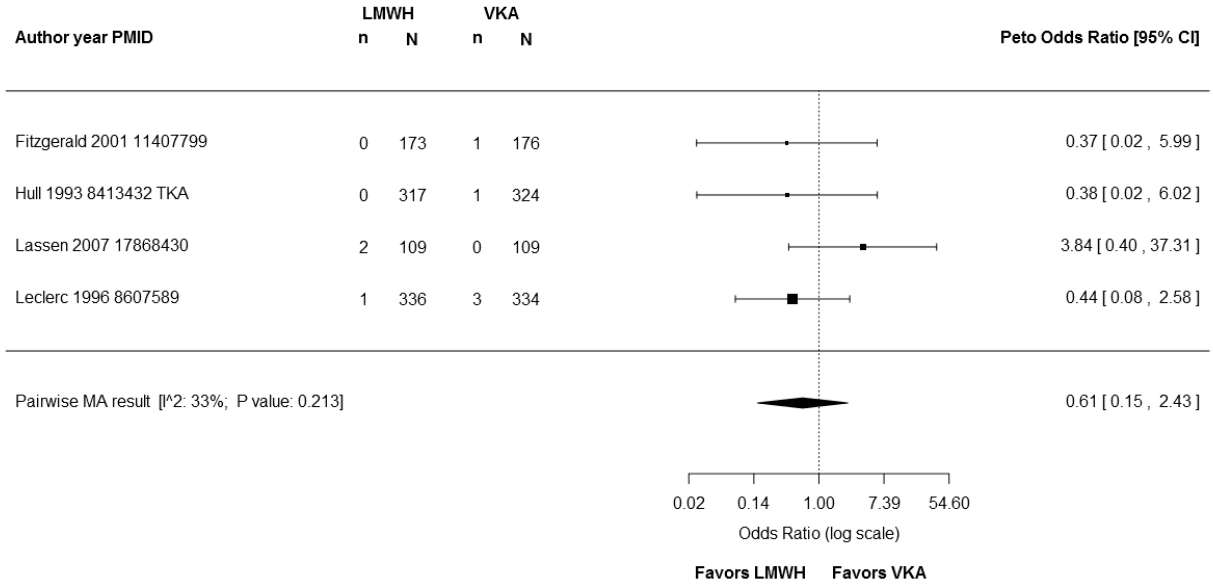
LMWH Versus VKA

Four RCTs (N=1960) compared LMWH versus VKA.[75, 99, 100] All four reported on VTE-related outcomes.

Total PE

Four RCTs (N=1878) reported total PE for the comparison of LMWH and VKA (0-1.8% in LMWH, 0-0.9% in VKA).[75, 99-101] Three RCTs[75, 99, 100] had a lower rate in the LMWH group. Meta-analysis of the four RCTs found an imprecise, nonsignificant estimate of OR for the risk of total PE between the two drug classes (summary OR=0.61, 95% CI 0.15 to 2.43). Study results were homogeneous (I^2 = 33%, P = 0.21) (**Figure 1.tkr.8**).

Figure 1.tkr.8. Forest plot: Total PE, LMWH vs. VKA

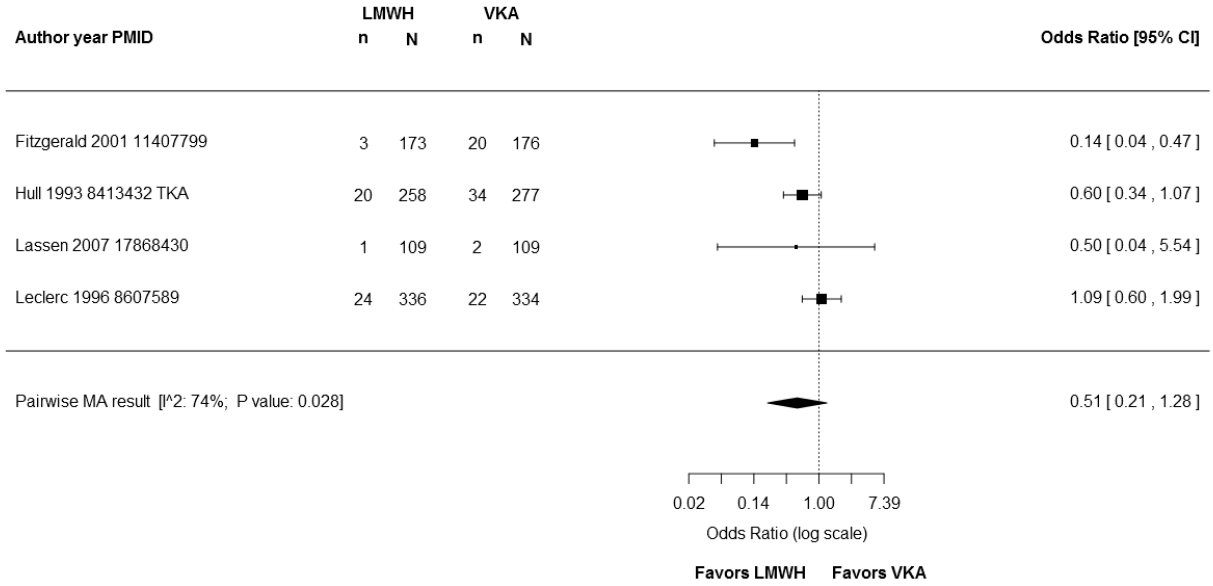


Forest plot of randomized controlled trials with calculated Peto odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with Peto fixed effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: LMWH = low molecular weight heparin, PMID = PubMed identifier, VKA = vitamin K antagonist.

Proximal DVT

Four RCTs[75, 99-101] (N=1772) comparing LMWH and VKA reported the occurrence of proximal DVT (0.9-7.8% in LMWH, 1.8-12.3% in VKA). The event rate was lower in the LMWH group in three RCTs,[75, 99, 101] statistically significantly so in one.[99] No significant difference was shown for the risk of proximal DVT between the two groups in the meta-analysis of the four RCTs (summary OR=0.51, 95% CI 0.21 to 1.28). There was substantial heterogeneity across the RCTs (I^2 = 74%, P = 0.028) (**Figure 1.tkr.9**). No clear explanation of the statistical heterogeneity could be found; however, doses and regimens varied across RCTs.

Figure 1.tkr.9. Forest plot: Proximal DVT, LMWH vs. VKA



Forest plot of randomized controlled trials with calculated Peto odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with Peto fixed effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: LMWH = low molecular weight heparin, PMID = PubMed identifier, VKA = vitamin K antagonist.

Other VTE Events

Two RCTs found no significant difference between the two classes in symptomatic VTE.[75, 100] Three RCTs reported no fatal PE events.[75, 99, 100] Three RCTs all found significantly fewer total DVT in the LMWH group (range of ORs: 0.42 [95% CI 0.27 to 0.66] to 0.67 [95% CI 0.48 to 0.94]).[75, 99, 100] One RCT found no significant difference in symptomatic DVT.[101]

Adverse Events

Four RCTs reported major bleeding, but one had no major bleeding events; the remaining three studies found no significant difference between classes.[75, 99-101] Three RCTs reported fatal bleeding, but two studies had no fatal bleeding events; the remaining study found no significant difference between intervention classes.[75, 99, 100] One study reported no episodes of bleeding leading to reoperation, infection leading to reoperation, or reoperation due to bleeding or infection.[99] This study also found no significant differences in bleeding at surgical site and 30-day mortality.[99]

Adherence

No studies reported adherence data.

VKA Versus Mechanical Devices

A U.S.-based registry NRCS of 25,388 TKR patients found a significant difference in total PE between warfarin and mechanical devices, favoring warfarin (OR 0.46, 95% CI 0.26 to 0.83), controlling for age, sex, anesthesia risk category, and use of general anesthesia (**Appendix Table F4**).[30]

Table X2. Results summary: Total knee replacement, intervention class vs. class comparisons

Comparison	Outcome	Studies, N	OR, 1 *(Summary OR)*	OR, 2	OR, 3	No Events*
Antiplatelet vs. FXaI	PE, Total	1	No estimate			1 RCT
	DVT, Total	1	**6.46 (1.84, 22.6)**			
	DVT, Symptomatic	1	4.72 (0.22, 99.6)			
	Wound complication	1	0.36 (0.07, 1.89)			
Antiplatelet vs. Mechanical	DVT, Total	1	**2.52 (1.20, 5.31)**			
	DVT, Proximal	1	0.52 (0.05, 5.87)			
Antiplatelet vs. VKA	DVT, Total	1	0.88 (0.47, 1.66)			
	DVT, Proximal	1	1.08 (0.42, 2.74)			
DTI vs. FXaI	PE, Total	1	No estimate			1 RCT
	DVT, Total	1	No estimate			1 RCT
	Bleeding, Major	1	No estimate			1 RCT
LMWH vs. Antiplatelet	PE, Total	1	No estimate			1 RCT
	DVT, Total	1	0.73 (0.34, 1.55)			
	DVT, Symptomatic	1	0.49 (0.04, 5.44)			
	Wound complication	1	1.49 (0.24, 9.07)			
LMWH vs. DTI	PE, Total	2	2.96 (0.12, 72.8)			1 RCT
	PE, Fatal	2	2.96 (0.12, 72.8)			
	PE, Symptomatic	1	No estimate			1 RCT
	DVT, Total	2	**2.30 (1.21, 4.38)**			1 RCT
	DVT, Symptomatic	3	0.67 (0.21, 2.12)	1.00 (0.06, 16.5)	7.96 (0.99, 63.9)	
	DVT, Proximal	2	0.67 (0.29, 1.51)	5.58 (0.66, 47.4)		
	Bleeding, Major	*5 (MA)*	*0.96 (0.43, 2.16)*			1 RCT
	Bleeding, Fatal	2	No estimate			2 RCTs
	Bleeding, Leading to reoperation	1	0.33 (0.03, 3.13)			
	Bleeding, Surgical site/joint	1	**5.49 (1.21, 24.8)**			
	Mortality, 30 day or in-hospital	1	0.99 (0.06, 15.8)			
LMWH vs. FXaI	*VTE, Total*	*4 (MA)*	*1.33 (0.89, 1.99)*			
	VTE, Symptomatic	3	0.25 (0.03, 2.26)	0.82 (0.21, 3.12)	2.02 (0.69, 5.95)	
	PE, Total	5	0.14 (0.02, 1.16)	1.67 (0.40, 7.04)	2.59 (0.29, 23.4)	2 RCTs
	PE, Fatal	5	0.20 (0.01, 4.16)	1.00 (0.06, 16.0)		3 RCTs
	PE, Symptomatic	3	2.07 (0.19, 23.2)	2.97 (0.12, 73.8)		1 RCT
	DVT, Total	*7 (MA)*	***2.09 (1.70, 2.58)***			1 RCT
	DVT, Symptomatic	*8 (MA)*	*0.99 (0.51, 1.91)*			

Comparison	Outcome	Studies, N	OR, 1 *(Summary OR)*	OR, 2	OR, 3	No Events*
	DVT, Proximal	*5 (MA)*	*1.32 (0.62, 2.82)*			
	Bleeding, Major	*7 (MA)*	*0.74 (0.42, 1.30)*			1 RCT
	Bleeding, Fatal	1	No estimate			1 RCT
	Bleeding, Leading to reoperation	1	0.50 (0.05, 5.52)			
	Bleeding, Surgical site/joint	2	0.33 (0.07, 1.67)	1.37 (0.55, 3.42)		
	Mortality, 30 day or in-hospital	3	0.20 (0.01, 4.16)	1.50 (0.25, 9.03)		1 RCT
	Adverse event, Serious	*4 (MA)*	*1.51 (0.80, 2.85)*			
	Readmission, bleeding or infection (combined)	1	0.24 (0.03, 2.18)			
	Wound complication	1	0.53 (0.12, 2.29)			
LMWH vs. FXIi	VTE, Total	1	1.28 (0.68, 2.41)			
	VTE, Symptomatic	1	0.98 (0.09, 11.0)			
	PE, Fatal	1	No estimate			1 RCT
	PE, Symptomatic	1	No estimate			1 RCT
	DVT, Total	1	1.28 (0.68, 2.41)			
	DVT, Symptomatic	1	0.98 (0.09, 11.0)			
	DVT, Proximal	1	1.43 (0.44, 4.67)			
	Bleeding, Major	1				1 RCT
	Adverse event, Serious	1	0.28 (0.01, 5.47)			
LMWH vs. Mechanical	PE, Fatal	1	0.21 (0.01, 4.32)			
	DVT, Total	1	0.86 (0.48, 1.54)			
	DVT, Proximal	1	0.12 (0.01, 2.23)			
	Bleeding, Fatal	1	No estimate			1 RCT
	Mortality, 30 day or in-hospital	1	0.34 (0.04, 3.34)			
LMWH vs. UFH	PE, Total	2	0.20 (0.01, 4.10)			1 RCT
	PE, Fatal	2	0.33 (0.01, 8.08)			
	DVT, Total	2	0.63 (0.42, 0.94)	0.80 (0.41, 1.57)		
	DVT, Symptomatic	1	0.33 (0.01, 8.29)			
	DVT, Proximal	2	0.21 (0.08, 0.56)	0.59 (0.14, 2.56)		
	Bleeding, Major	1	0.99 (0.20, 4.94)			
	Bleeding, Surgical site/joint	1	1.81 (0.60, 5.48)			
LMWH vs. VKA	VTE, Symptomatic	2	1.02 (0.06, 16.4)	3.00 (0.31, 29.0)		
	PE, Total	*4 (MA)*	*0.61 (0.15, 2.43)*			
	PE, Fatal	3	No estimate			3 RCTs
	DVT, Total	3	**0.42 (0.27, 0.66)**	**0.60 (0.43, 0.85)**	**0.67 (0.48, 0.94)**	

Comparison	Outcome	Studies, N	OR, 1 *(Summary OR)*	OR, 2	OR, 3	No Events*
	DVT, Symptomatic	1	1.00 (0.06, 16.2)			
	DVT, Proximal	*4 (MA)*	*0.51 (0.21, 1.28)*			
	Bleeding, Major	4	1.16 (0.39, 3.50)	2.36 (0.71, 7.81)	3.13 (0.84, 11.7)	1 RCT
	Bleeding, Fatal	3	0.34 (0.01, 8.33)			2 RCTs
	Bleeding, Leading to reoperation	1	No estimate			1 RCT
	Bleeding, Surgical site/joint	1	2.11 (0.77, 5.76)			
	Mortality, 30 day or in-hospital	1	0.34 (0.03, 3.25)			
	Return to OR, bleeding or infection (combined)	1	No estimate			1 RCT
	Infection, Leading to reoperation	1	No estimate			1 RCT

All outcomes for all pairwise comparisons with data from at least one study. If 3 or fewer randomized controlled trials (RCT) with analyzable data (i.e., at least 1 event per study) then each study's odds ratio (OR) is listed in ascending order from left to right. If there were ≥4 analyzable studies, then meta-analysis was conducted and summary OR is reported. These are indicated by italics and by MA (meta-analysis) in the study number column. Statistically significant OR estimates are in bold text. The corresponding studies for each analysis can be found in Appendix F.

Other abbreviations: DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venothromboembolism, Antiplatelet = antiplatelet agent, FXaI = factor Xa inhibitor, Mechanical = mechanical devices, VKA = vitamin K antagonist, DTI = direct thrombin inhibitor, LMWH = low molecular weight heparin, FXIi = factor XI inhibitor, UFH = unfractionated heparin.

* Number of RCTs with no events in both arms.

Cross-Study Subgroup Analyses

As noted at the start of the Results section, studies were generally homogeneous in terms of patient eligibility criteria, such that most across-study comparisons of subgroup factors are limited.

Among TKR RCTs, differences between studies based on industry funding was analyzable for only the comparison of LMWH versus FXaI. For total DVT, by random effects model metaregresion no significant difference (P=0.21) was found between the six industry-funded studies (summary OR 2.04, 95% CI 1.68 to 2.49) and the single study without industry support (OR 4.71, 95% CI 1.31 to 16.9).

For the comparison of Asian versus non-Asian RCTs, only the comparison of LMWH versus FXaI was analyzable. For total DVT, no significant difference (P=0.97) was found between the four Asian studies (summary OR 2.15, 95% CI 1.35 to 3.41) and three non-Asian studies (summary OR 2.12, 95% CI 1.59 to 2.82) by random effects model metaregresion. However, the total DVT rate was lower in the Asian RCTs (9.6%) than the non-Asian studies (16.0%, P<0.01). Similarly, for major bleeding, no significant difference (P=0.34) was found between the two Asian studies (summary OR 0.27, 95% CI 0.03 to 2.32) and the five non-Asian studies (OR 0.89, 95% CI 0.29 to 2.72). Major bleeding rates were similar between Asian studies (0.7%) and non-Asian studies (0.9%, P=0.57).

Hip Fracture Surgery

The results summary table (**Table X3**) is presented at the end of the HFx surgery section. It includes results for all reported comparisons and outcomes from HFx surgery RCTs. The reader should refer to this table for each results section summary even though the table is not repeatedly cited in each section. Where data are summarized only appendix tables or are summarized in figures, these are cited.

Antiplatelet Drug Versus Mechanical Device

One RCT compared an antiplatelet drug versus a mechanical device.[102] No significant differences were found between arms for total PE, total DVT, and symptomatic DVT. No adverse events or adherence data were reported.

Antiplatelet Drug Versus VKA

One RCT compared an antiplatelet drug versus VKA.[103] The study found no significant differences in total PE and fatal PE (all patients with PE died). There was no significant difference in major bleeding events and no patient had a fatal bleed. Adherence data were not reported.

LMWH Versus FXaI

Three RCTs (N=1816) compared LMWH versus FXaI.[104-106] Two studies evaluated VTE; one found no significant difference in total VTE and no symptomatic VTE events; the other found no significant difference in symptomatic VTE. All three reported on PE. One found no significant difference in total PE; two had no symptomatic PE events; and one study found no difference in fatal PE while another had no fatal PE events. The three studies also reported on DVT. Two of three studies found that patients treated with LMWH were significantly more likely to have total DVTs, but the third study found no significant difference in which more

patients treated with FXaI had total DVT (range of ORs: 0.55 [95% CI 0.05 to 5.58] to 3.81 [95% CI 1.22 to 11.9]).

All three studies found no significant difference in major bleeding (range of ORs: 0.18[95% CI 0.01 to 3.91] to 2.07 [95% CI 0.12 to 34.4]). One study found no significant difference in fatal bleeding while a second reported no occurrences of fatal bleeding. One study found no significant difference in bleeding leading to reoperation.

One study found no significant difference in serious adverse events and another no significant difference in 30-day mortality.

No study reported adherence data.

LMWH Versus UFH

One RCT compared LMWH versus UFH.[107] The study found no significant difference in total PEs, with no fatal PEs occurring. Total DVTs were just-significantly more likely to occur in patients treated with LMWH. The study found a similar, but nonsignificant estimate of effect for proximal DVTs.

The study found nonsignificant differences between arms for fatal bleeding and 30-day mortality. No adherence data were reported.

Table X3. Results summary: Hip fracture surgery, intervention class vs. class comparisons

Comparison	Outcome	Studies, N	OR, 1 *(Summary OR)*	OR, 2	OR, 3	No Events*
Antiplatelet vs. Mechanical	PE, Total	1	2.92 (0.12, 72.8)			
	DVT, Total	1	1.75 (0.49, 6.26)			
	DVT, Symptomatic	1	1.97 (0.35, 11.2)			
Antiplatelet vs. VKA	PE, Total	1	3.00 (0.12, 75.0)			
	PE, Fatal	1	3.00 (0.12, 75.0)			
	Bleeding, Major	1	0.18 (0.02, 1.63)			
	Bleeding, Fatal	1	No estimate			1 RCT
LMWH vs. FXaI	VTE, Total	1	0.55 (0.05, 5.58)			
	VTE, Symptomatic	2	0.75 (0.36, 1.56)			1 RCT
	PE, Total	1	0.99 (0.43, 2.29)			
	PE, Fatal	2	0.86 (0.31, 2.39)			1 RCT
	PE, Symptomatic	2	No estimate			2 RCTs
	DVT, Total	3	0.55 (0.05, 5.58)	**2.71 (1.90, 3.87)**	**3.81 (1.22, 11.9)**	
	DVT, Symptomatic	2	0.99 (0.06, 15.8)			1 RCT
	DVT, Proximal	3	2.00 (0.17, 23.4)	**4.86 (2.00, 11.8)**		1 RCT
	Bleeding, Major	3	0.18 (0.01, 3.91)	1.04 (0.54, 2.00)	2.07 (0.12, 34.4)	
	Bleeding, Fatal	2	2.96 (0.12, 72.9)			1 RCT
	Bleeding, Leading to reoperation	1	0.66 (0.11, 3.94)			
	Mortality, 30 day or in-hospital	1	1.10 (0.70, 1.72)			
	Adverse event, Serious	1	2.15 (0.41, 11.4)			
LMWH vs. UFH	PE, Total	1	14.3 (0.78, 262)			
	PE, Fatal	1	No estimate			1 RCT
	DVT, Total	1	**3.11 (1.00, 9.68)**			
	DVT, Proximal	1	3.00 (0.91, 9.94)			
	Bleeding, Fatal	1	0.31 (0.01, 7.86)			
	Mortality, 30 day or in-hospital	1	0.62 (0.10, 3.91)			

All outcomes for all pairwise comparisons with data from at least one study. If 3 or fewer randomized controlled trials (RCT) with analyzable data (i.e., at least 1 event per study) then each study's odds ratio (OR) is listed in ascending order from left to right. If there were ≥4 analyzable studies, then meta-analysis was conducted and summary OR is reported. These are indicated by italics and by MA (meta-analysis) in the study number column. Statistically significant OR estimates are in bold text. The corresponding studies for each analysis can be found in Appendix F.
Other abbreviations: DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venothromboembolism, Antiplatelet = antiplatelet agent, Mechanical = mechanical devices, VKA = vitamin K antagonist, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, UFH = unfractionated heparin.
* Number of RCTs with no events in both arms.

Key Question 2

In patients undergoing major orthopedic surgery, what is the comparative efficacy of individual thromboprophylaxis interventions within classes on venous thromboembolism outcomes, major bleeding, other adverse events, and treatment adherence?

Note that for all three surgeries, network meta-analyses comparing individual interventions in regard to total DVT and major bleeds are presented under Key Question 5.

Total Hip Replacement

The results summary table (**Table X4**) is presented at the end of the THR section. It includes results for all reported comparisons and outcomes from THR RCTs. The reader should refer to this table for each results section summary even though the table is not repeatedly cited in each section. Where data are summarized only appendix tables or are summarized in figures, these are cited.

LMWH: Enoxaparin Versus Semuloparin

One RCT compared the LMWHs enoxaparin versus semuloparin.[108] The study found significantly more total DVTs with enoxaparin than semuloparin, but no significant difference in proximal DVTs.

The study also found significantly more episodes of major bleeding with enoxaparin than semuloparin. No study participants had a fatal bleed. There were no significant differences in 30-day mortality or serious adverse events.

The study did not evaluate adherence.

LMWH: Enoxaparin Versus Tinzaparin

One RCT compared the LMWHs enoxaparin versus tinzaparin.[109] All VTE-related outcomes were not significantly different in both arms, including total PE, fatal PE, total DVT, symptomatic DVT, and proximal DVT.

There were also no significant differences in major bleeding and surgical site bleeding, and no fatal bleeding events. There were no significant differences in 30-day mortality or heparin-induced thrombocytopenia.

The study did not evaluate adherence.

Mechanical: GCS Versus IPC

Two RCTs (N=161) compared GCS versus IPC; in one RCT all participants also received enoxaparin.[110, 111] One NRCS (N=1533) also compared GCS versus active compression devices (**Appendix Table F4**).[23] One RCT reported no PEs or symptomatic DVTs. The other RCT found no significant difference in total DVTs. Both RCTs found no significant difference in proximal DVTs. The NRCS did not run statistical analyses, but the 0.4 percent had a PE with an active compression device and 0 percent for GCS.

The studies did not report bleeding, other adverse events, or adherence results.

Table X4. Results summary: Total hip replacement, within-class intervention vs. intervention comparisons

Comparison	Outcome	Studies, N	OR, 1 *(Summary OR)*	OR, 2	OR, 3	No Events*
LMWH: Enoxaparin vs. Semuloparin	DVT, Total	1	**1.85 (1.32, 2.60)**			
	DVT, Proximal	1	1.15 (0.54, 2.42)			
	Bleeding, Major	1	**3.52 (1.16, 10.7)**			
	Bleeding, Fatal	1	No estimate			1 RCT
	Mortality, 30 day or in-hospital	1	2.00 (0.18, 22.1)			
	Adverse event, Serious	1	1.35 (0.85, 2.16)			
LMWH: Enoxaparin vs. Tinzaparin	PE, Total	1	2.03 (0.18, 22.6)			
	PE, Fatal	1	3.05 (0.12, 75.2)			
	DVT, Total	1	0.91 (0.57, 1.44)			
	DVT, Symptomatic	1	1.52 (0.25, 9.19)			
	DVT, Proximal	1	1.12 (0.60, 2.08)			
	Bleeding, Major	1	2.04 (0.37, 11.3)			
	Bleeding, Fatal	1	No estimate			1 RCT
	Bleeding, Surgical site/joint	1	2.04 (0.37, 11.3)			
	Mortality, 30 day or in-hospital	1	3.05 (0.12, 75.2)			
	Heparin-induced thrombocytopenia	1	3.05 (0.12, 75.2)			
Mechanical: GCS vs. IPC	PE, Total	1	No estimate			1 RCT
	DVT, Symptomatic	1	No estimate			1 RCT
(+Enoxaparin both arms)	DVT, Total	1	12.3 (0.63, 239)			
(±Enoxaparin both arms)	DVT, Proximal	2	3.24 (0.96, 11.0)	3.65 (0.14, 93.3)		

All outcomes for all pairwise comparisons with data from at least one study. If 3 or fewer randomized controlled trials (RCT) with analyzable data (i.e., at least 1 event per study) then each study's odds ratio (OR) is listed in ascending order from left to right. If there were ≥4 analyzable studies, then meta-analysis was conducted and summary OR is reported. These are indicated by italics and by MA (meta-analysis) in the study number column. Statistically significant OR estimates are in bold text. The corresponding studies for each analysis can be found in Appendix F.
Other abbreviations: DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venothromboembolism, LMWH = low molecular weight heparin, Mechanical = mechanical devices, GCS = graduated compression stockings, IPC = Intermittent Pneumatic Compression.
* Number of RCTs with no events in both arms.

Total Knee Replacement

The results summary table (**Table X5**) is presented after the HFx surgery section. It includes results for all reported comparisons and outcomes from TKR RCTs. The reader should refer to this table for each results section summary even though the table is not repeatedly cited in each section. Where data are summarized only appendix tables or are summarized in figures, these are cited.

LMWH: Enoxaparin Versus Semuloparin

One RCT compared the LMWHs enoxaparin versus semuloparin.[108] The study found no significant differences in total or proximal DVTs.

The study also found no significant difference in major bleeding. No study participants had a fatal bleed or 30-day mortality. There was no significant difference in serious adverse events.

The study did not evaluate adherence.

LMWH: Enoxaparin Versus Tinzaparin

One RCT compared the LMWHs enoxaparin versus tinzaparin.[84] However, the study participants had no PEs, DVTs, or major bleeding events. The study did not evaluate adherence.

Mechanical: GCS Versus IPC

One RCT compared GCS versus IPC, in which all participants also received enoxaparin.[111] The study found many more total DVTs in the GCS group than the IPC group (14/35 vs. 0/35; OR 47.9, 95% CI 2.72, 844), but no significant difference in proximal DVTs (although still favoring IPC).

The study did not report bleeding, other adverse events, or adherence results.

Mechanical: TED Hose Versus Non-TED Mechanical Devices

A U.S.-based registry NRCS of 25,388 TKR patients found no significant difference in total PE between those using TED hose and other mechanical devices (OR 0.48, 95% CI 0.06 to 3.51), controlling for age, sex, anesthesia risk category, and use of general anesthesia (**Appendix Table F4**).[30]

Hip Fracture Surgery

The results summary table (**Table X6**) is presented at the end of the HFx surgery section. It includes results for all reported comparisons and outcomes from HFx surgery RCTs. The reader should refer to this table for each results section summary even though the table is not repeatedly cited in each section. Where data are summarized only appendix tables or are summarized in figures, these are cited.

LMWH: Enoxaparin Versus Dalteparin

One RCT compared the LMWHs enoxaparin versus dalteparin.[112] The study participants had no PEs or symptomatic DVTs. The rates of total DVT and proximal DVT were not significantly different between drugs.

The study found no significant difference in major bleeding or surgical site bleeding between LMWHs.

The study did not evaluate adherence.

LMWH: Enoxaparin Versus Semuloparin

One RCT compared the LMWHs enoxaparin and semuloparin.[108] The study found no significant difference in total DVTs, but significantly more proximal DVTs with enoxaparin.

There was no significant difference in major bleeding between LMWHs and no fatal bleeding events in either arm. Serious adverse events and 30-day mortality were not significantly different between arms.

The study did not evaluate adherence.

Table X5. Results summary: Total knee replacement, within-class intervention vs. intervention comparisons

Comparison	Outcome	Studies, N	OR, 1 *(Summary OR)*	OR, 2	OR, 3	No Events*
LMWH: Enoxaparin vs. Semuloparin	DVT, Total	1	1.20 (0.89, 1.63)			
	DVT, Proximal	1	0.57 (0.26, 1.27)			
	Bleeding, Major	1	1.35 (0.30, 6.05)			
	Bleeding, Fatal	1	No estimate			1 RCT
	Mortality, 30 day or in-hospital	1	No estimate			1 RCT
	Adverse event, Serious	1	1.33 (0.64, 2.76)			
LMWH: Enoxaparin vs. Tinzaparin	PE, Total	1	No estimate			1 RCT
	DVT, Total	1	No estimate			1 RCT
	Bleeding, Major	1	No estimate			1 RCT
Mechanical: GCS vs. IPC (+Enoxaparin both arms)	DVT, Total	1	**47.9 (2.72, 844)**			
	DVT, Proximal	1	3.09 (0.12, 78.4)			

All outcomes for all pairwise comparisons with data from at least one study. If 3 or fewer randomized controlled trials (RCT) with analyzable data (i.e., at least 1 event per study) then each study's odds ratio (OR) is listed in ascending order from left to right. If there were ≥4 analyzable studies, then meta-analysis was conducted and summary OR is reported. These are indicated by italics and by MA (meta-analysis) in the study number column. Statistically significant OR estimates are in bold text. The corresponding studies for each analysis can be found in Appendix F.
Other abbreviations: DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venothromboembolism, LMWH = low molecular weight heparin, Mechanical = mechanical devices, GCS = graduated compression stockings, IPC = Intermittent Pneumatic Compression.
* Number of RCTs with no events in both arms.

Table X6. Results summary: Hip fracture surgery, within-class intervention vs. intervention comparisons

Comparison	Outcome	Studies, N	OR, 1 *(Summary OR)*	OR, 2	OR, 3	No Events*
LMWH: Enoxaparin vs. Dalteparin	PE, Total	1	No estimate			1 RCT
	DVT, Total	1	1.89 (0.58, 6.20)			
	DVT, Symptomatic	1	No estimate			1 RCT
	DVT, Proximal	1	0.72 (0.12, 4.49)			
	Bleeding, Major	1	2.03 (0.18, 23.0)			
	Bleeding, Surgical site/joint	1	0.33 (0.01, 8.21)			
LMWH: Enoxaparin vs. Semuloparin	DVT, Total	1	1.38 (0.95, 1.99)			
	DVT, Proximal	1	**2.10 (1.06, 4.14)**			
	Bleeding, Major	1	0.58 (0.14, 2.46)			
	Bleeding, Fatal	1	No estimate			1 RCT
	Mortality, 30 day or in-hospital	1	0.49 (0.09, 2.67)			
	Adverse event, Serious	1	0.94 (0.55, 1.62)			

All outcomes for all pairwise comparisons with data from at least one study. If 3 or fewer randomized controlled trials (RCT) with analyzable data (i.e., at least 1 event per study) then each study's odds ratio (OR) is listed in ascending order from left to right. If there were ≥4 analyzable studies, then meta-analysis was conducted and summary OR is reported. These are indicated by italics and by MA (meta-analysis) in the study number column. Statistically significant OR estimates are in bold text. The corresponding studies for each analysis can be found in Appendix F.
Other abbreviations: DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venothromboembolism, LMWH = low molecular weight heparin.
* Number of RCTs with no events in both arms.

Key Question 3

In patients undergoing major orthopedic surgery, what is the comparative efficacy of different doses, regimens, or treatment durations of the same thromboprophylaxis interventions on venous thromboembolism outcomes, major bleeding, other adverse events, and treatment adherence?

Different Doses or Regimens

The narrative here describes comparisons of doses for each intervention that were addressed by two or more studies. The more than 300 specific comparison-outcome pairs that were evaluated by only a single study are presented only in Appendix F.

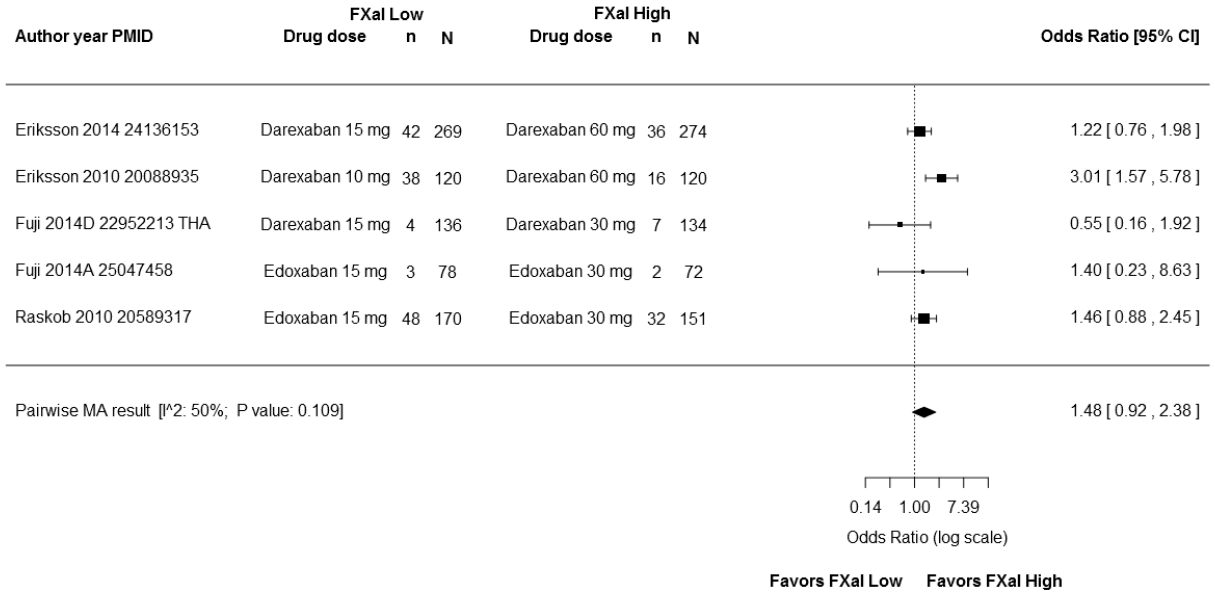
Total Hip Replacement

The results summary table (**Table X7**) is presented at the end of the THR section. It includes results for reported comparisons and outcomes from THR RCTs with at least two studies. The reader should refer to this table for each results section summary even though the table is not repeatedly cited in each section. The reader should also refer to Appendix F for comparisons evaluated by only one study.

FXaI

Five RCTs (N=1524) comparing FXaI low versus high doses reported total VTE (2.9-31.7% for low dose, 2.8-21.2% for high dose).[49-52, 56] The rate was significantly lower in the high dose group in one study.[52] Meta-analysis of the five studies found no significant difference between the two dose groups for the risk of total VTE (summary OR=1.48, 95% CI 0.92 to 2.38) (**Figure 3dose.thr.1**). There was possible heterogeneity across the studies (I^2 = 50%, P = 0.11).

Figure 3dose.thr.1. Forest plot: Total VTE, FXaI, low versus high dose



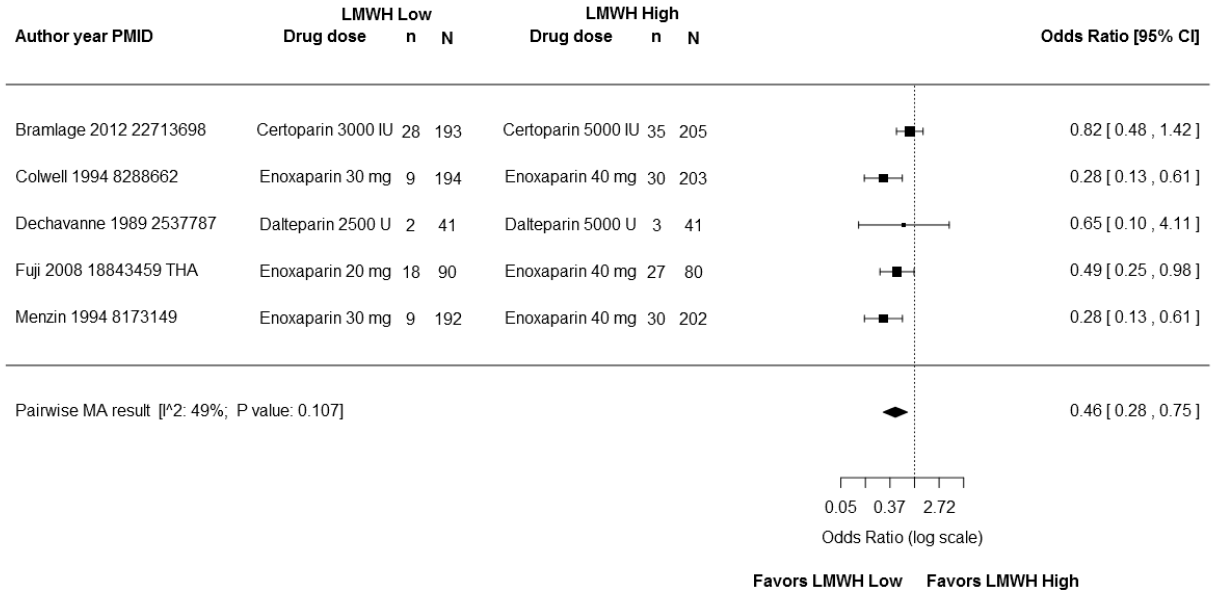
Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: FXaI = factor Xa inhibitor,, PMID = PubMed identifier, VTE = venothromboembolism.

LMWH

Total DVT

Five RCTs (N=1441) reported total DVT for the comparison of low versus high doses of LMWH (4.6-20.0% for low dose, 7.3-33.8% for high dose).[67-69, 113, 114] The rate was lower in the low dose group in all the RCTs and statistically significant in three.[68, 69, 114] Meta-analysis of the five RCTs yielded a summary OR of 0.46 (95% CI 0.28 to 0.75) for the risk of total DVT, significantly favoring the low dose group (**Figure 3dose.thr.2**). There was possible statistical heterogeneity across the RCTs (I^2 = 49%, P = 0.11).

Figure 3dose.thr.2. Forest plot: Total DVT, LMWH, low versus high dose

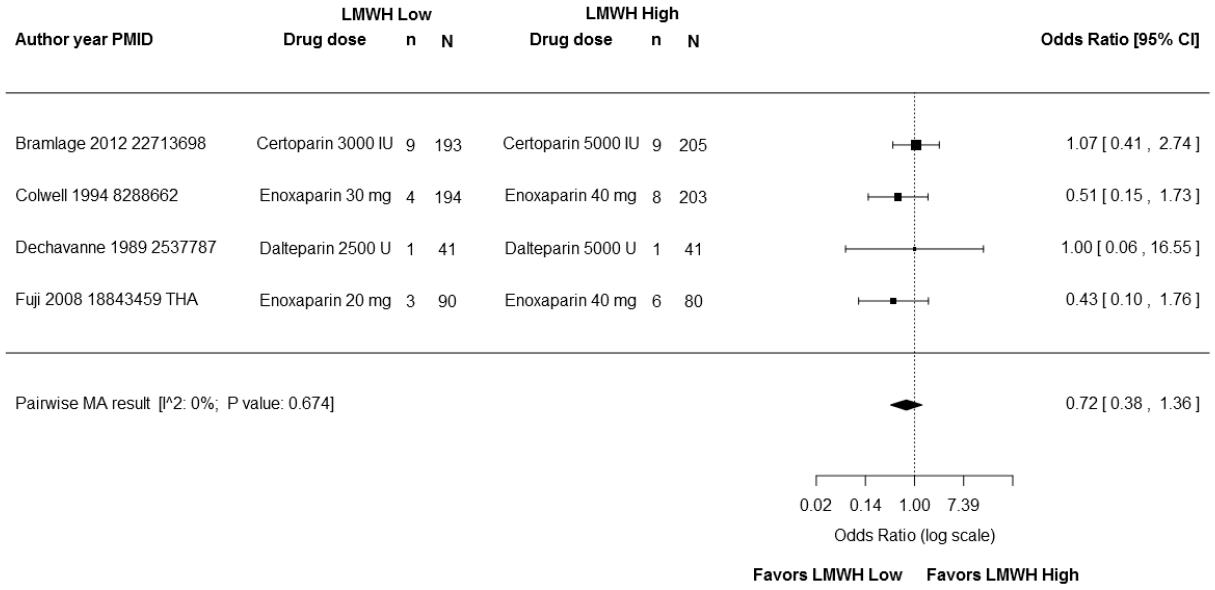


Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: DVT = deep vein thrombosis, LMWH = low molecular weight heparin, PMID = PubMed identifier.

Proximal DVT

Four RCTs (N=1047) that assessed relative effectiveness of low versus high doses of LMWH reported proximal DVT (2.1-4.7% for low dose, 2.4-7.5% for high dose).[67, 69, 113, 114] Two RCTs showed a lower rate in the low dose group.[69, 114] No significant difference was shown for the risk of proximal DVT between the two doses in the meta-analysis of the four RCTs (summary OR=0.72, 95% CI 0.38 to 1.36). Study results were homogeneous (I^2 = 0%, P = 0.67) (**Figure 3dose.thr.3**).

Figure 3dose.thr.3. Forest plot: Proximal DVT, LMWH, low versus high dose

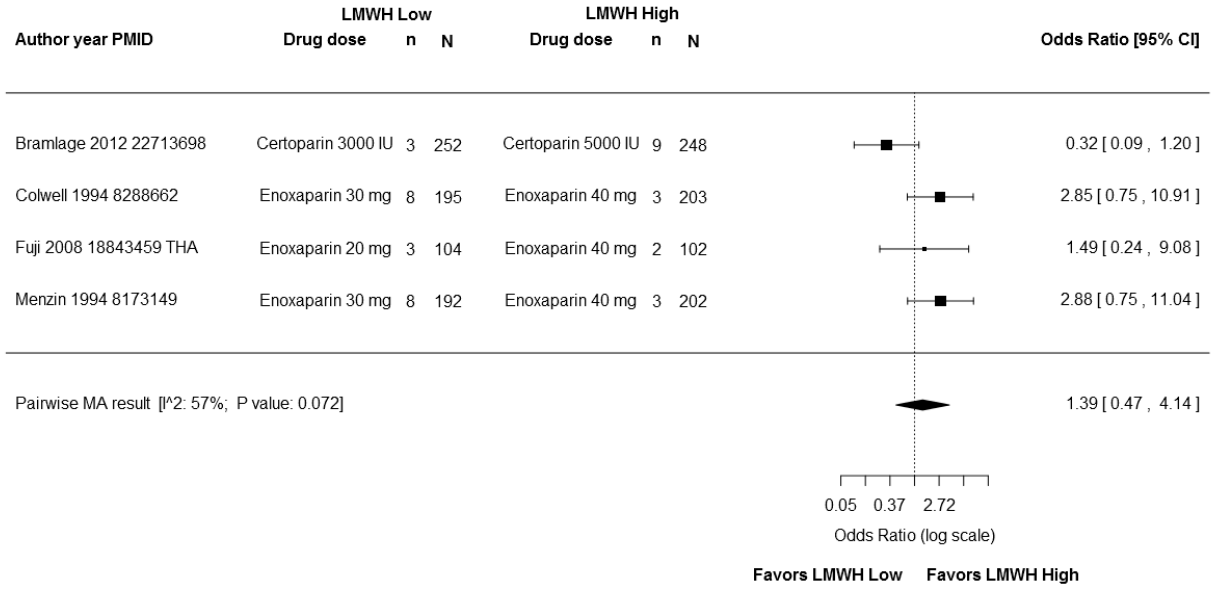


Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: DVT = deep vein thrombosis, LMWH = low molecular weight heparin, PMID = PubMed identifier.

Major Bleeding

Four RCTs (N=1498) that compared low versus high doses of LMWH reported major bleeding (1.2-4.2% in high dose group, 1.5-3.6% in low dose group).[68, 69, 113, 114] The rate of bleeding was lower in the high dose group in three RCTs.[68, 69, 114] Meta-analysis of the four RCTs found an imprecise estimate of OR with no significant difference for the risk of major bleeding between the two doses (summary OR=1.39, 95% CI 0.47 to 4.14). There was heterogeneity across the RCTs (I^2 = 57%, P = 0.072) (**Figure 3dose.thr.4**). No clear explanation of the statistical heterogeneity could be found; however, specific drugs, doses, and regimens varied across RCTs.

Figure 3dose.thr.4. Forest plot: Major bleeding, LMWH, low versus high dose



Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: LMWH = low molecular weight heparin, PMID = PubMed identifier.

Dabigatran

Two RCTs (N=2845) compared different doses (150 mg vs. 220 or 225 mg) of dabigatran.[45, 46] The studies found no significant difference between the two dose groups regarding major bleeding.

Darexaban

Two RCTs (N=835) compared darexaban 15 mg versus 30 mg twice daily.[49, 51] No significant difference was found in total VTE in the two studies.

Two RCTs (N=801) compared darexaban 30 mg versus 60 mg once daily.[51, 52] The studies found no significant difference in total VTE, and reported no fatal PEs.

Edoxaban

Two RCTs (N=536) compared edoxaban 15 mg and 30 mg once daily.[50, 56] The two studies found no significant difference in total VTE and major bleeding, and reported no symptomatic PE events. One RCT reported no proximal DVTs and no serious adverse events. The other found no significant differences in proximal DVTs or in serious adverse events.

Enoxaparin

Two RCTs (N=792) compared enoxaparin 40 mg once daily and 30 mg every 12 hours.[68, 69] The two studies found significantly fewer total DVT in the low dose group, while no significant difference was found in major bleeding.

Intermittent Pneumatic Compression

Three RCTs compared three different regimens of mechanical devices (**Appendix F1**). One RCT (N=54) compared IPC with adjusted versus fixed cycling rates reported adherence.[115] The rate was adjusted every 30 minutes according to the individual refill time of both legs in the first group, while the rate was fixed at 90 cycles per hour in the other group. The study found no significant difference in total DVT, proximal DVT, and adherence between the two groups. During followup, 100 percent of patients received full-time pneumatic compression as scheduled (good adherence) in both groups.

One RCT (N=24) compared IPC with alternate sequential compression versus continuous sequential compression of both legs.[116] The study found no significant difference in total DVT, and reported no proximal DVT and no symptomatic DVT events.

One RCT (N=423) compared two different brands (Kendal vs. venaflow) of IPC devices.[117] The study found significant fewer total DVT in the venaflow group, but found no significant difference in total PE, proximal DVT, and 30-day mortality. The study reported no no fatal PE, symptomatic DVT, and no fatal bleeding.

Table X7. Results summary: Total hip replacement, dose comparisons

Comparison	Outcome	Studies, N	Patients, N	OR, 1	OR, 2	OR, 3	No Events*
Dabigatran 150 mg vs. Dabigatran 220 or 225 mg	Bleeding, Major	2	2845	0.64 (0.33, 1.23)	0.84 (0.36, 1.98)		
Darexaban 15 mg BID vs. Darexaban 30 mg BID	VTE, Total	2	835	0.55 (0.16, 1.92)	1.47 (0.90, 2.41)		
Darexaban 30 mg qD vs. Darexaban 60 mg qD	VTE, Total	2	801	1.02 (0.62, 1.65)	1.55 (0.77, 3.14)		
	PE, Fatal	2	801	No estimate			2 RCTs
Edoxaban 15 mg vs. Edoxaban 30 mg	VTE, Total	2	471	1.40 (0.23, 8.63)	1.46 (0.88, 2.45)		
	PE, Symptomatic	2	471	No estimate			2 RCTs
	DVT, Proximal	2	471	2.02 (0.69, 5.95)			1 RCT
	Bleeding, Major	2	536	0.31 (0.01, 7.83)	0.88 (0.05, 14.3)		
	Adverse event, serious	2	536	1.43 (0.46, 4.47)			1 RCT
Enoxaparin 30 mg vs. Enoxaparin 40 mg	DVT, Total	2	791	**0.28 (0.13, 0.61)**	**0.28 (0.13, 0.61)**		
	Bleeding, Major	2	792	2.85 (0.75, 10.9)	2.88 (0.75, 11.0)		

All outcomes for all pairwise comparisons with data from at least two studies. Each study's odds ratio (OR) is listed in ascending order from left to right. Statistically significant OR estimates are in bold text. The corresponding studies for each analysis can be found in Appendix F.
Other abbreviations: DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venothromboembolism, mg = milligram.
* Number of RCTs with no events in both arms.

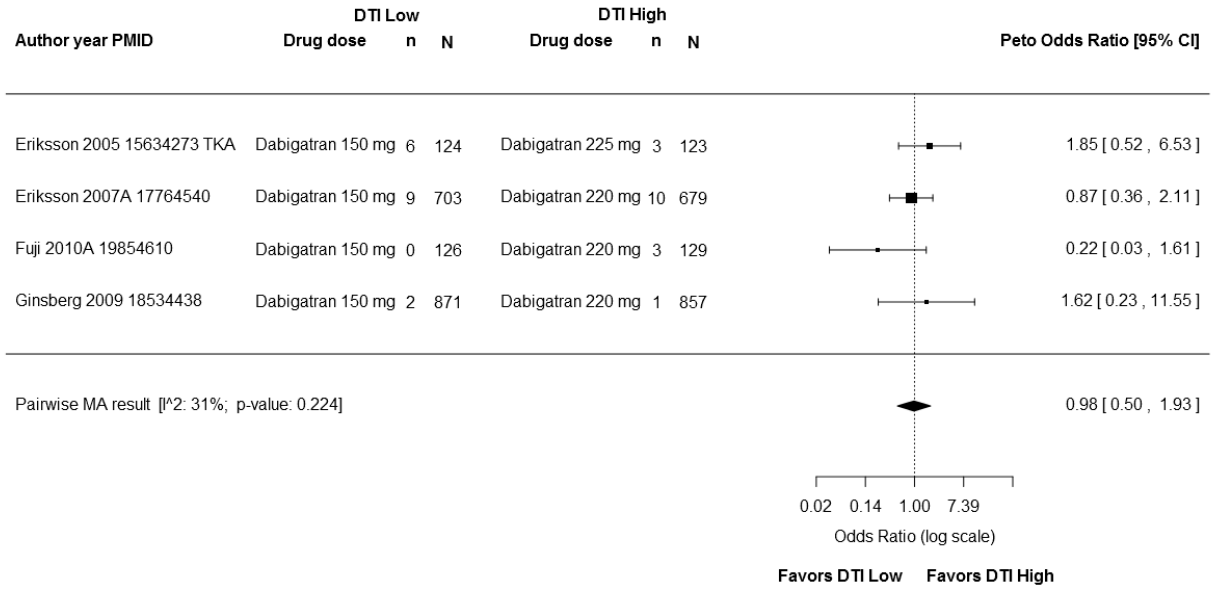
Total Knee Replacement

The results summary table (**Table X8**) is presented at the end of the TKR section. It includes results for reported comparisons and outcomes from TKR RCTs with at least two studies. The reader should refer to this table for each results section summary even though the table is not repeatedly cited in each section. The reader should also refer to Appendix F2 for comparisons evaluated by only one study.

DTI

Four RCTs (N=3612) reported major bleeding for the comparison of low versus high doses for DTI (0-4.8% in low dose, 0.1-2.4% in high dose).[46, 60, 85, 86] Two RCTs[46, 86] had a lower rate in the high dose group. No significant difference was shown for the risk of major bleeding between the two doses by meta-analysis of the four RCTs (summary OR=0.98, 95% CI 0.50 to 1.93). Study results were homogeneous (I^2 = 31%, P = 0.22) (**Figure 3dose.tkr.1**).

Figure 3dose.tkr.1. Forest plot: Major bleeding, DTI, low versus high dose



Forest plot of randomized controlled trials with calculated Peto odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with Peto fixed effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: DTI = direct thrombin inhibitor, PMID = PubMed identifier.

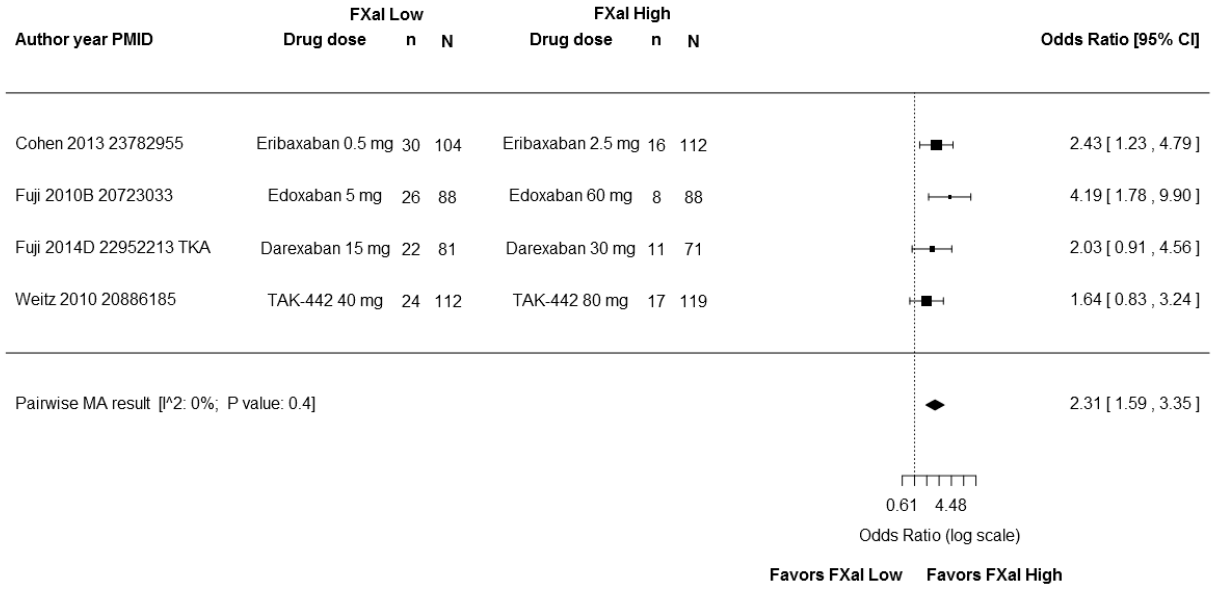
FXaI

Total VTE

Four RCTs (N=775) that examined relative effectiveness of low versus high doses of FXaI reported total VTE (21.4-29.6% in low dose, 9.1-15.5% in high dose).[49, 93, 94, 118] Patients who received FXaI at high doses had a lower rate of VTE in all the RCTs, which was statistically

significant in two.[94, 118] Meta-analysis of the four RCTs yielded a summary OR of 2.31 (95% CI 1.59 to 3.35) for the risk of total VTE, significantly favoring the high dose group. Study results were homogeneous (I^2 = 0%, P = 0.40) (**Figure 3dose.tkr.2**).

Figure 3dose.tkr.2. Forest plot: Total VTE, FXaI, low versus high dose

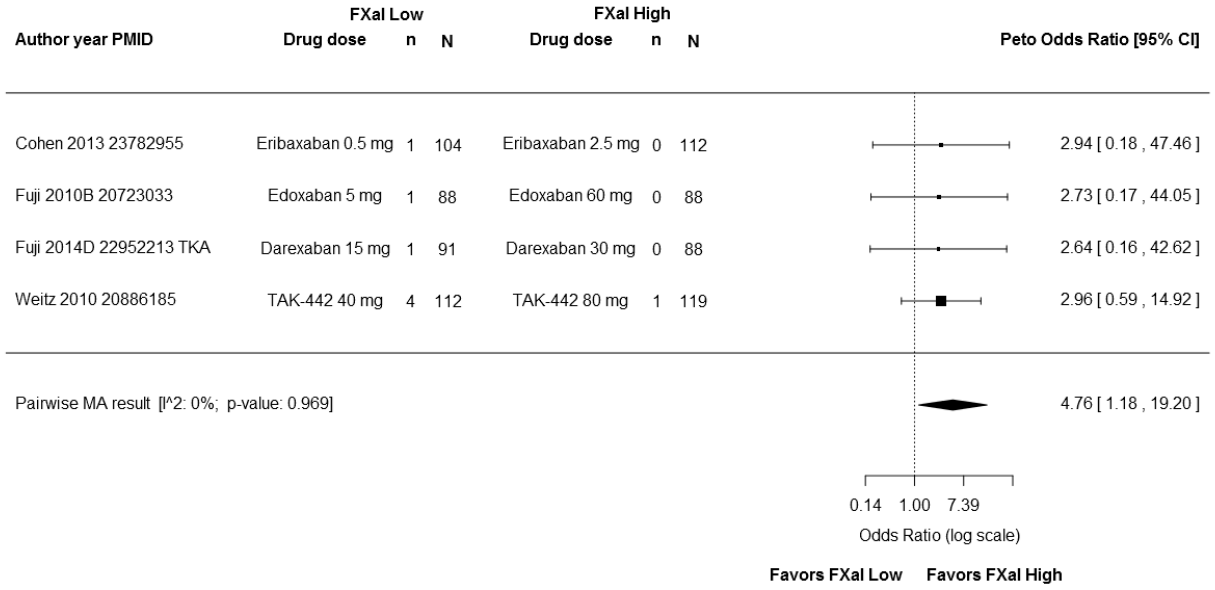


Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: FXaI = factor Xa inhibitor, PMID = PubMed identifier, VTE = venous thromboembolism.

Symptomatic DVT

Four RCTs (N=802) assessing low versus high doses of FXaI reported the outcome of symptomatic DVT (1.0-3.6% in low dose, 0-0.8% in high dose).[49, 93, 94, 118] All the four RCTs had a lower rate in the high dose group. Meta-analysis of the four RCTs yielded a summary OR of 4.76 (95% CI 1.18 to 19.2), significantly favoring the high dose group. Study results were homogeneous (I^2 = 0%, P = 0.97) (**Figure 3dose.tkr.3**).

Figure 3dose.tkr.3. Forest plot: Symptomatic DVT, FXaI, low versus high dose

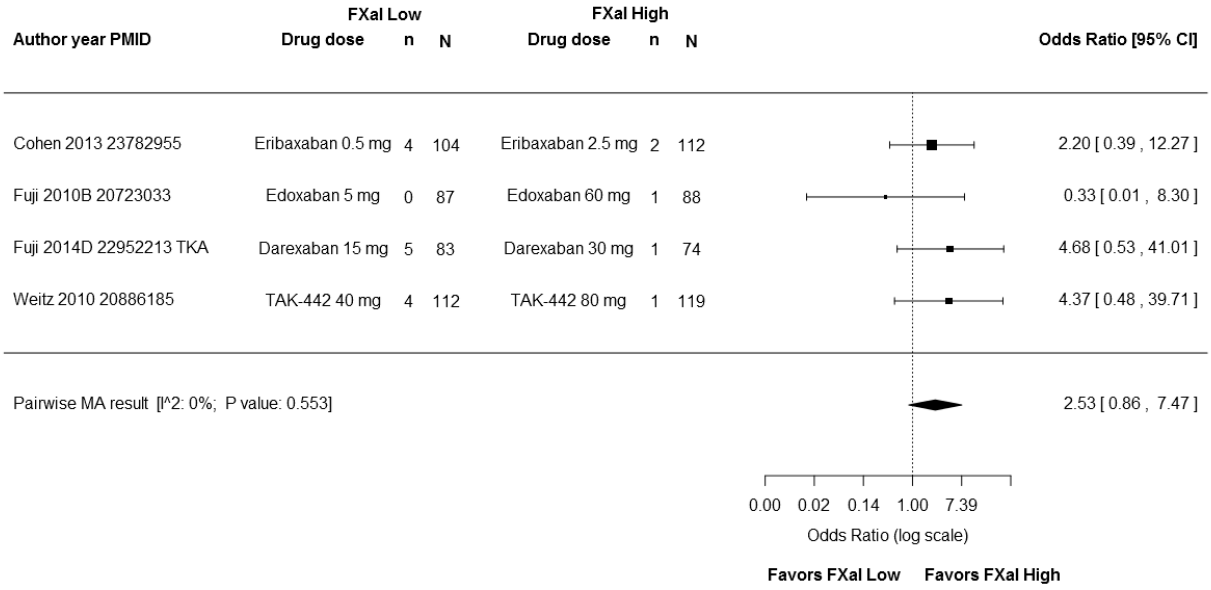


Forest plot of randomized controlled trials with calculated Peto odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with Peto fixed effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: DVT = deep vein thrombosis, FXaI = factor Xa inhibitor PMID = PubMed identifier.

Proximal DVT

Four RCTs (N=779) that assessed low versus high doses of FXaI reported proximal DVT (0-6.0% in low dose, 0.8-1.8% in high dose).[49, 93, 94, 118] The rate was lower in the high dose group in three RCTs.[49, 93, 94] Meta-analysis of the four RCTs yielded no significant difference for the risk of proximal DVT between the two doses (summary OR=2.53, 95% CI 0.86 to 7.47). Study results were homogeneous (I^2 = 0%, P = 0.55) (**Figure 3dose.tkr.4**).

Figure 3dose.tkr.4. Forest plot: Proximal DVT, FXaI, low versus high dose

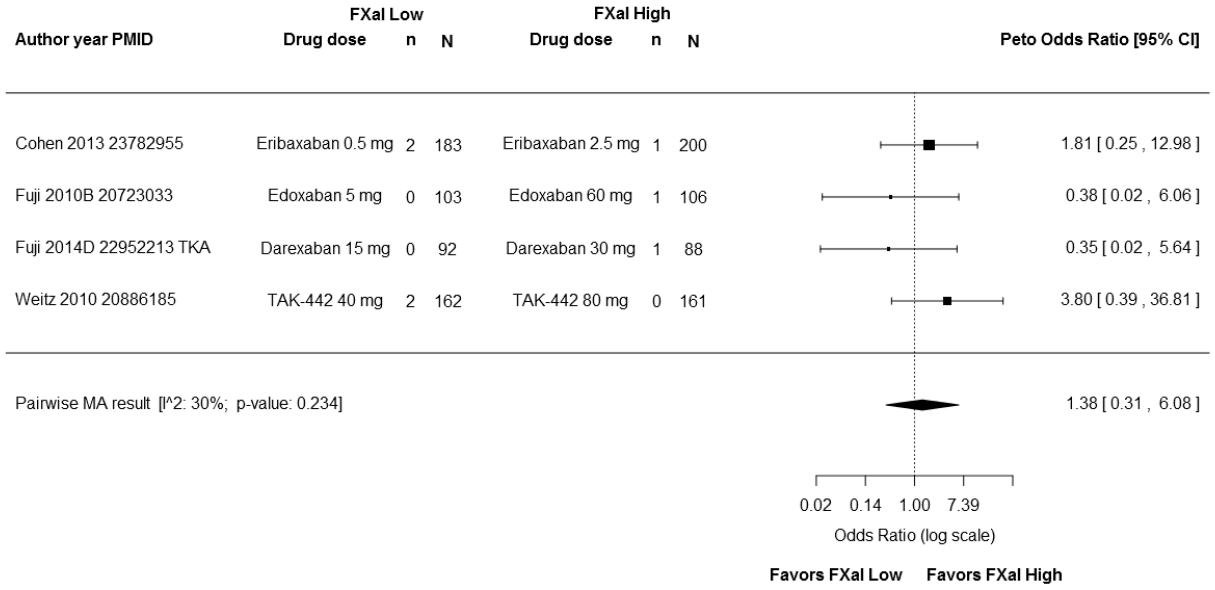


Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: DVT = deep vein thrombosis, FXaI = factor Xa inhibitor, PMID = PubMed identifier.

Major Bleeding

Four RCTs (N=1095) that compared low versus high doses of FXaI reported major bleeding (0-1.2% in low dose, 0-1.1% in high dose).[49, 93, 94, 118] The rate was lower in the high dose group in two RCTs.[93, 94] Meta-analysis of the four RCTs found an imprecise estimate of OR with no significant difference for the risk of major bleeding between the two doses (summary OR=1.38, 95% CI 0.31 to 6.08). Study results were homogeneous (I^2 = 30%, P = 0.23) (**Figure 3dose.tkr.5**).

Figure 3dose.tkr.5. Forest plot: Major bleeding, FXaI, low versus high dose



Forest plot of randomized controlled trials with calculated Peto odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with Peto fixed effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: FXaI = factor Xa inhibitor, PMID = PubMed identifier.

Dabigatran

Three RCTs (N=3365) compared dabigatran 150 mg daily and 220 mg daily.[60, 85, 86] Two studies reported total PEs, but one had no PE events; the other found no significant difference in PE events. Two studies reported no fatal PE events. The three RCTs found no significant difference in symptomatic DVT (range of ORs: 0.80 [95% CI 0.27 to 2.38] to 2.92 [95% CI 0.30 to 28.1]). Two studies found no significant difference in proximal DVT.

The three RCTs found no significant difference in major bleeding (range of ORs: 0.14 [95% CI 0.01 to 2.79] to 0.98 [95% CI 0.28 to 3.41]), and reported no fatal bleeding. The three studies reported bleeding leading to reoperation, but one had no such events; the remaining two found no significant differences. The three studies also reported 30-day mortality, with no mortality in one and no significant difference in two.

Edoxaban

One RCT[50] comparing high versus low doses of edoxaban reported adherence. At 11 to 14 days of followup, 100 percent of patients were adherent to their prescriptions in both dose groups.

Table X8. Results summary: Total knee replacement, dose comparisons

Comparison	Outcome	Studies, N	Patients, N	OR, 1	OR, 2	OR, 3	No Events*
Dabigatran 150 mg vs. Dabigatran 220 mg	PE, Total	2	1626	2.91 (0.12, 71.7)			1 RCT
	PE, Fatal	2	1626	No estimate			2 RCTs
	DVT, Symptomatic	3	2879	0.80 (0.27, 2.38)	2.06 (0.18, 23.1)	2.92 (0.30, 28.1)	
	DVT, Proximal	2	1468	1.34 (0.67, 2.68)	4.60 (0.22, 96.9)		
	Bleeding, Major	3	3365	0.14 (0.01, 2.79)	0.87 (0.35, 2.15)	0.98 (0.28, 3.41)	
	Bleeding, Fatal	3	3365	No estimate			3 RCTs
	Bleeding, Leading to reoperation	3	3365	0.32 (0.03, 3.09)	0.34 (0.01, 8.39)		1 RCT
	Mortality, 30 day or in-hospital	3	3354	0.97 (0.06, 15.5)	0.98 (0.06, 15.8)		1 RCT

All outcomes for all pairwise comparisons with data from at least two studies. Each study's odds ratio (OR) is listed in ascending order from left to right. Statistically significant OR estimates are in bold text. The corresponding studies for each analysis can be found in Appendix F.
Other abbreviations: DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venothromboembolism, mg = milligram.
* Number of RCTs with no events in both arms.

Hip Fracture Surgery

None of the studies of HFx surgery compared different intervention doses or regimens.

Different Treatment Durations

Total Hip Replacement

The results summary table (**Table X9**) is presented at the end of the THR section. It includes results for reported comparisons and outcomes from THR RCTs. The reader should refer to this table for each results section summary even though the table is not repeatedly cited in each section. NRCS are summarized in **Appendix Tables F5**.

Various Anticoagulation Interventions

Two NRCSs reported on total VTE in patients undergoing THR (**Appendix Table F4)**. Both evaluated different durations of treatment in large cohorts who had received a variety of anticoagulation types. Wells 2010 reported no significant differences among anticoagulation durations of 14, 21, and 28 days that favored longer prophylaxis.[26] Pedersen 2015 reported slightly fewer VTE events with anticoagulation of more than 28 days than with short (0 to 6 days) or standard (7 to 27 days) duration. Once adjusted for age, sex, Charlson Comorbidity Index score, anticoagulation drug and use of acetylsalicylic acid, other antiplatelet drugs, and warfarin use prior to THR, no significant differences were found between short and extended duration (>28 days; HR 0.83, 95% CI 0.52 to 1.31) or between standard and extended durations (HR 0.82, 95% CI 0.50 to 1.33).[24]

In an NRCS, Wells 2010 compared PE rates across timepoints of varied anticoagulant interventions (**Appendix Table F4**). The NRCS reported no significant differences among anticoagulation durations of 14, 21, and 28 days.[26]

In a NRCS, Wells 2010 compared DVT rates across timepoints of varied anticoagulant interventions.[26] The NRCS reported no significant differences among anticoagulation durations of 14, 21, and 28 days (**Appendix Table F4**).

FXaI

One RCT (N=40) compared rivaroxaban given for short and long durations,[53] but reported no total DVTs.

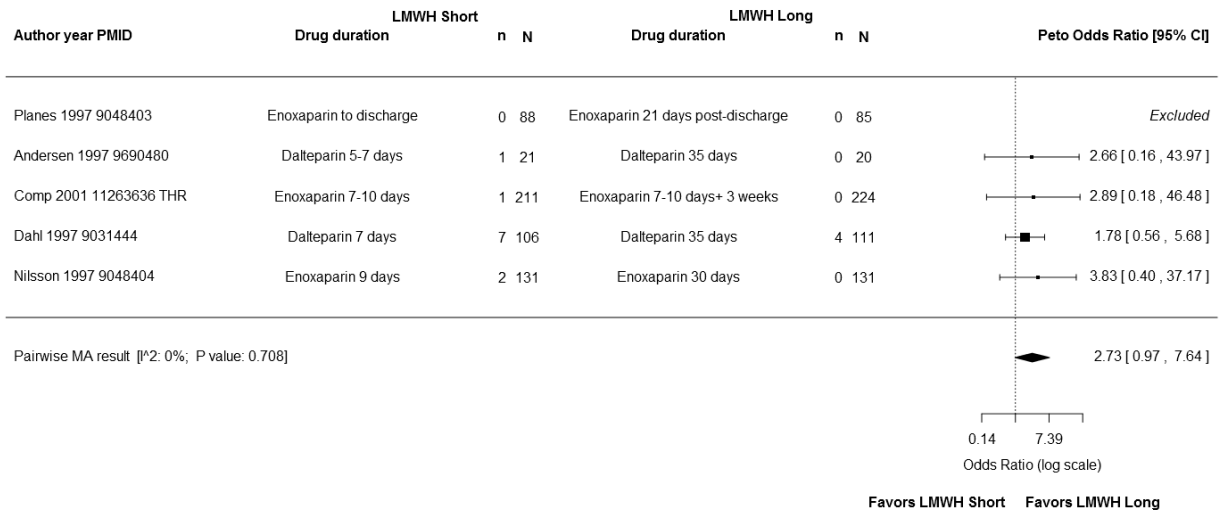
LMWH

Six RCTs (N=1463) compared LMWH of short versus long durations.[119-124]

Total PE

Five RCTs (N=1128) reported total PE for the comparison of short versus long therapeutic durations of LMWH (0-6.6% for short duration, 0-3.6% for long duration).[119-123] One RCT reported no occurrence of PE in either comparison group.[121] Patients who received LMWH for long duration had a lower event rate in the remaining four RCTs. Meta-analysis of the four RCTs found an almost-significant difference between the two treatment durations for the risk of total PE (summary OR=2.73, 95% CI 0.97 to 7.64), favoring long duration (**Figure 3duration.thr.1**). Study results were homogeneous ($I^2 = 0\%$, $P = 0.71$).

Figure 3duration.thr.1. Forest plot: Total PE, LMWH, short versus long duration

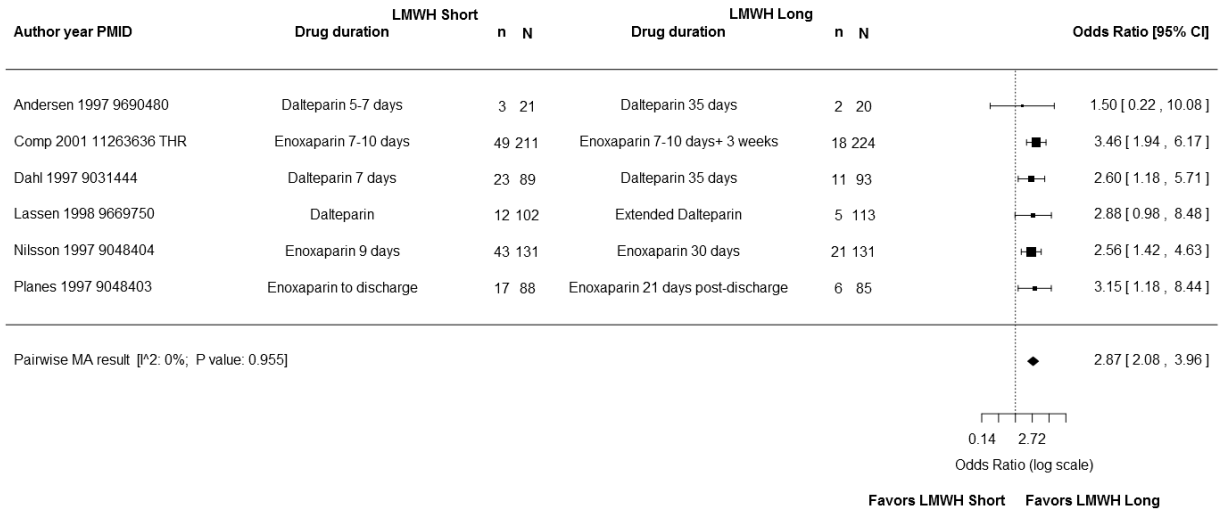


Forest plot of randomized controlled trials with calculated Peto odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with Peto fixed effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: LMWH = low molecular weight heparin, PE = pulmonary embolism, PMID = PubMed identifier.

Total DVT

Six RCTs (N=1308) reported total DVT and examined short versus long therapeutic durations of LMWH (11.8-32.8% for short duration, 4.4-16.0% for long duration).[119-124] Patients who received LMWH of long duration had a lower event rate in all the RCTs, statistically significantly so in four.[119-122] Meta-analysis of the six RCTs yielded a summary OR of 2.87 (95% CI 2.08 to 3.96) for the risk of total DVT, significantly favoring the long duration group. Study results were homogeneous (I^2 = 0%, P = 0.96) (**Figure 3duration.thr.2**).

Figure 3duration.thr.2. Forest plot: Total DVT, LMWH, short versus long duration

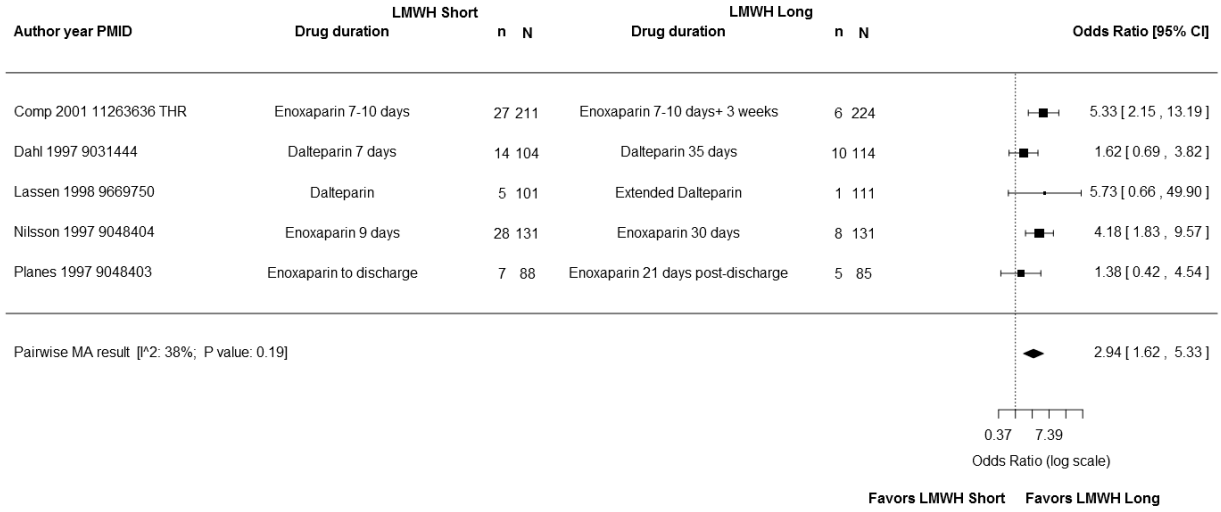


Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: DVT = deep vein thrombosis, LMWH = low molecular weight heparin, PMID = PubMed identifier.

Proximal DVT

Five RCTs (N=1300) reported proximal DVT for the comparison of short versus long therapeutic durations of LMWH (5.0-21.4% for short duration, 0.9-8.8% for long duration).[119-122, 124] The rate was lower in the long duration group in all the RCTs, which was statistically significant in two.[119, 120] Meta-analysis of the five RCTs yielded a summary OR of 2.94 (95% CI 1.62 to 5.33) for the risk of proximal DVT, significantly favoring the long duration group. Study results were homogeneous (I^2 = 38%, P = 0.19) (**Figure 3duration.thr.3**).

Figure 3duration.thr.3. Forest plot: Proximal DVT, LMWH, short versus long duration



Forest plot of randomized controlled trials with calculated Peto odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with Peto fixed effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: DVT = deep vein thrombosis, LMWH = low molecular weight heparin, PMID = PubMed identifier.

Other VTE Events

Two RCTs found significantly fewer symptomatic VTE in the long duration group.[119, 120] Four RCTs reported fatal PE; one found no significant difference, and three reported no incidents of fatal PE.[119-122] Three RCTs found no significant difference in symptomatic DVT.[120, 122, 123]

Adverse Events

Three RCTs reported on major bleeding, with no significant difference in one and no incidents of major bleeding in two studies.[119, 121, 124] Four studies reported no fatal bleeding. Three RCTs reported 30-day mortality; one found no significant difference, and two reported no mortality.[119, 121, 122] One study found no significant difference in reoperation due to bleeding or infection.[123]

Adherence

No study reported on adherence

VKA

One RCT (N=360) compared short versus long therapeutic durations of warfarin.[125] The study found no significant difference in symptomatic VTE, total PE, total DVT, symptomatic DVT, proximal DVT, and major bleeding, and reported no fatal PE and no fatal bleeding. The study did not report on adherence.

Table X9. Results summary: Total hip replacement, duration comparisons

Comparison	Outcome	Studies, N	Patients, N	OR, 1	OR, 2	OR, 3	No Events*
FXaI_Short vs. FXaI_Long	DVT, Total	1	40	No estimate			1 RCT
LMWH_Short vs. LMWH_Long	VTE, Symptomatic	2	697	**3.46 (1.94, 6.17)**	**5.33 (1.14, 24.8)**		
	PE, Total	*5 (MA)*	*1128*	*2.73 (0.97, 7.64)*			1 RCT
	PE, Fatal	4	1087	3.17 (0.13, 78.7)			3 RCTs
	DVT, Total	*6 (MA)*	*1308*	***2.87 (2.08, 3.96)***			
	DVT, Symptomatic	3	521	0.53 (0.15, 1.81)	0.95 (0.06, 16.3)	4.20 (0.87, 20.2)	
	DVT, Proximal	*5 (MA)*	*1300*	***2.94 (1.62, 5.33)***			
	Bleeding, Major	3	895	3.00 (0.12, 74.3)			2 RCTs
	Bleeding, Fatal	4	1135	No estimate			4 RCTs
	Mortality, 30 day or in-hospital	3	873	1.02 (0.06, 16.5)			2 RCTs
	Return to OR, bleeding or infection	1	41	5.26 (0.24, 117)			
VKA_Short vs. VKA_Long	VTE, Symptomatic	1	360	3.25 (0.87, 12.2)			
	PE, Total	1	360	3.15 (0.13, 77.9)			
	PE, Fatal	1	360	No estimate			1 RCT
	DVT, Total	1	360	2.87 (0.75, 11.0)			
	DVT, Symptomatic	1	360	1.58 (0.26, 9.56)			
	DVT, Proximal	1	360	3.17 (0.33, 30.8)			
	Bleeding, Major	1	360	0.35 (0.01, 8.56)			
	Bleeding, Fatal	1	360	No estimate			1 RCT

All outcomes for all pairwise comparisons with data from at least one study. If 3 or fewer randomized controlled trials (RCT) with analyzable data (i.e., at least 1 event per study) then each study's odds ratio (OR) is listed in ascending order from left to right. If there were ≥4 analyzable studies, then meta-analysis was conducted and summary OR is reported. These are indicated by italics and by MA (meta-analysis) in the study number column. Statistically significant OR estimates are in bold text. The corresponding studies for each analysis can be found in Appendix F.

Other abbreviations: DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venothromboembolism, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, VKA = vitamin K antagonist, Short vs. Long = short therapeutic duration versus long duration.

* Number of RCTs with no events in both arms.

Total Knee Replacement

The results summary table (**Table X10**) is presented at the end of the Key Question 3 section. It includes results for reported comparisons and outcomes from TKR RCTs. The reader should refer to this table for each results section summary even though the table is not repeatedly cited in each section. As noted, NRCS are summarized in **Appendix Tables F5**.

LMWH

One RCT (N=438) compared enoxaparin of short versus long therapeutic durations.[119] The study found no significant difference in symptomatic VTE, total PE, total DVT, proximal DVT, and major bleeding, and reported no fatal PE, no fatal bleeding, and no 30-day mortality. The study did not report on adherence.

Hip Fracture Surgery

The results summary table (**Table X11**) is presented at the end of the HFx surgery section. It includes results for reported comparisons and outcomes from HFx surgery RCTs. The reader should refer to this table for each results section summary even though the table is not repeatedly cited in each section. As noted, NRCS are summarized in **Appendix Tables F6**.

FXaI

One RCT (N=656) compared fondaparinux for short and long therapeutic durations.[126] The study found significantly more frequent symptomatic VTE (OR 9.11, 95% CI 1.15 to 72.3), total DVT (OR 35.1, 95% CI 10.9 to 113.6), and proximal DVT (OR 20.5, 95% 4.86 to 86.4) in the short duration group. No significant differences were found for total PE, fatal PE, and symptomatic DVT.

The study found no significant difference in major bleeding, fatal bleeding, bleeding leading to reoperation, and bleeding at surgical site or joint, and reported no bleeding leading to infection. The study did not report on adherence.

LMWH

One RCT (N=469) compared semuloparin of short versus long durations.[127] The study found significantly fewer total DVT and proximal DVT in the long duration group. No significant difference was found in fatal PE, major bleeding, 30-day mortality, and serious adverse events. The study did not report on adherence.

Table X10. Results summary: Total knee replacement, duration comparisons

Comparison	Outcome	Studies, N	Patients, N	OR, 1	OR, 2	OR, 3	No Events*
LMWH_Short vs. LMWH_Long	VTE, Symptomatic	1	438	1.24 (0.77, 2.00)			
	PE, Total	1	438	4.95 (0.24, 104)			
	PE, Fatal	1	438	No estimate			1 RCT
	DVT, Total	1	438	1.24 (0.77, 2.00)			
	DVT, Proximal	1	438	1.93 (0.84, 4.42)			
	Bleeding, Major	1	438	2.96 (0.12, 73.0)			
	Bleeding, Fatal	1	438	No estimate			1 RCT
	Mortality, 30 day or in-hospital	1	438	No estimate			1 RCT

All outcomes for all pairwise comparisons with data from at least one study. If 3 or fewer randomized controlled trials (RCT) with analyzable data (i.e., at least 1 event per study) then each study's odds ratio (OR) is listed in ascending order from left to right. If there were ≥4 analyzable studies, then meta-analysis was conducted and summary OR is reported. These are indicated by italics and by MA (meta-analysis) in the study number column. Statistically significant OR estimates are in bold text. The corresponding studies for each analysis can be found in Appendix F.
Other abbreviations: DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venothromboembolism, LMWH = low molecular weight heparin, Short vs. Long = short therapeutic duration versus long duration.
* Number of RCTs with no events in both arms.

Table X11. Results summary: Hip fracture surgery, duration comparisons

Comparison	Outcome	Studies, N	Patients, N	OR, 1	OR, 2	OR, 3	No Events*
FXaI_Short vs. FXaI_Long	VTE, Symptomatic	1	656	**9.11 (1.15, 72.3)**			
	PE, Total	1	656	6.98 (0.36, 136)			
	PE, Fatal	1	656	2.97 (0.12, 73.2)			
	DVT, Total	1	426	**35.1 (10.9, 114)**			
	DVT, Symptomatic	1	656	6.02 (0.72, 50.3)			
	DVT, Proximal	1	443	**20.5 (4.86, 86.4)**			
	Bleeding, Major	1	656	0.24 (0.05, 1.16)			
	Bleeding, Fatal	1	656	1.33 (0.46, 3.89)			
	Bleeding, Leading to reoperation	1	656	0.99 (0.14, 7.10)			
	Bleeding, Surgical site/joint	1	656	0.08 (<0.01, 1.34)			
	Bleeding, Leading to infection	1	656	No estimate			1 RCT
LMWH_Short vs. LMWH_Long	PE, Fatal	1	469	5.99 (0.24, 148)			
	DVT, Total	1	330	**5.03 (2.16, 11.7)**			
	DVT, Proximal	1	394	**6.23 (1.94, 20.0)**			
	Bleeding, Major	1	469	0.66 (0.03, 16.3)			
	Mortality, 30 day or in-hospital (AE)	1	469	10.1 (0.48, 211)			
	Serious adverse event	1	469	2.38 (0.79, 7.21)			

All outcomes for all pairwise comparisons with data from at least one study. If 3 or fewer randomized controlled trials (RCT) with analyzable data (i.e., at least 1 event per study) then each study's odds ratio (OR) is listed in ascending order from left to right. If there were ≥4 analyzable studies, then meta-analysis was conducted and summary OR is reported. These are indicated by italics and by MA (meta-analysis) in the study number column. Statistically significant OR estimates are in bold text. The corresponding studies for each analysis can be found in Appendix F.
Other abbreviations: DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venothromboembolism, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, Short vs. Long = short therapeutic duration versus long duration.
* Number of RCTs with no events in both arms.

Key Question 4

In patients undergoing major orthopedic surgery, what is the comparative efficacy of combined classes of thromboprophylaxis interventions versus single classes on venous thromboembolism outcomes, major bleeding, other adverse events, and treatment adherence?

Note that for all three surgeries, network meta-analyses comparing individual interventions (including combination interventions) in regard to total DVT and major bleeds are presented under Key Question 5.

Total Hip Replacement

The results summary table (**Table X12**) is presented at the end of the Key Question 4 section. It includes results for all reported comparisons and outcomes from THR RCTs. The reader should refer to this table for each results section summary even though the table is not repeatedly cited in each section. Where data are summarized only appendix tables or are summarized in figures, these are cited.

Antiplatelet Drug Versus Combination Antiplatelet Drug and Mechanical Device

One RCT compared an antiplatelet drug alone versus combination antiplatelet drug and mechanical device.[128] The study found no significant difference in total PEs and no occurrences of fatal PE. The study also found no significant difference in proximal DVTs.

The study reported no episodes of fatal bleeding and found no significant difference in 30-day mortality between arms.

The study did not evaluate adherence.

LMWH Versus Combination LMWH and Antiplatelet Drug

One RCT compared LMWH to a combination of LMWH and an antiplatelet drug.[129] The study found no significant differences in VTE outcomes, including symptomatic VTE, symptomatic PE, symptomatic DVT, and proximal DVT. No patient had a fatal PE.

The study also found no significant difference in major bleeding, surgical site bleeding, or wound infection.

The study did not evaluate adherence.

LMWH Versus Combination LMWH and DTI

One RCT compared LMWH to a combination of LMWH and DTI.[39] The study reported only that there was no significant difference in total DVT. Adverse events and adherence were not reported.

LMWH Versus Combination LMWH and FXaI

The same RCT compared LMWH to a combination of LMWH and FXaI.[39] The study reported only that there was no significant difference in total DVT. Adverse events and adherence were not reported.

LMWH Versus Combination LMWH and Mechanical Device

Two RCTs compared LMWH to a combination of LMWH and a mechanical device.[130, 131] One of the studies reported no PEs. Both studies found no significant difference in total DVT. Regarding proximal DVT, one study had no such events and the other found no significant difference between arms.

One study reported no fatal bleeding events and no 30-day mortality. Neither study evaluated adherence.

Mechanical Device Versus Combination Mechanical Device and Antiplatelet Drug

One RCT compared a mechanical device alone versus a combination of a mechanical device and an antiplatelet drug.[38] The study found no significant difference in total PE or proximal DVTs. Adverse events and adherence were not reported.

Mechanical Device Versus Combination Mechanical Device and Antiplatelet Drug and UFH

One RCT compared a mechanical device alone versus a combination of a mechanical device, an antiplatelet drug, and UFH.[132] However, the study found no occurrences of DVT (total, symptomatic, or proximal), fatal bleeding, or 30-day mortality. The study did not report on adherence.

Mechanical Device Versus Combination Mechanical Device and VKA

One RCT compared a mechanical device versus a combination of a mechanical device and a VKA.[38] The study had no PEs and found no significant difference in proximal DVTs. Adverse events and adherence were not reported.

UFH Versus Combination UFH and LMWH

One RCT compared UFH alone versus combination UFH and LMWH.[133] The study reported only no significant difference in total DVT. Adverse events and adherence were not reported.

Combination UFH and Antiplatelet Drug Versus Combination UFH and Antiplatelet Drug and Mechanical Device

One RCT compared combination UFH and an antiplatelet drug with the further addition of a mechanical device.[132] The study found no significant differences in total DVT, symptomatic DVT, and proximal DVT.

The study had no episodes of fatal bleeding or 30-day mortality. The study did not report on adherence.

Total Knee Replacement

The results summary table (**Table X13**) is presented at the end of the Key Question 4 section. It includes results for all reported comparisons and outcomes from THR RCTs. The reader should refer to this table for each results section summary even though the table is not repeatedly cited in each section. Where data are summarized only appendix tables or are summarized in figures, these are cited.

Antiplatelet Drug Versus Combination Antiplatelet Drug and Mechanical Device

One RCT compared an antiplatelet drug alone versus a combination of an antiplatelet drug and a mechanical device.[134] The study found significantly more total DVTs in the antiplatelet drug alone arm, but no significant difference in proximal DVT (although still favoring the combination arm).

The study had no episodes of major bleeding and did not report on adherence.

LMWH Versus Combination LMWH and FEI

One RCT compared LMWH alone versus combination LMWH and FEI.[135] The study found that significantly more patients in the LMWH alone arm had total DVT. The studies reported no PE or episodes of symptomatic DVT. There was no significant difference in proximal DVT.

The study had no episodes of major bleeding and did not report on adherence.

LMWH Versus Combination LMWH and Mechanical Device

Three RCTs compared LMWH and combination LMWH and a mechanical device;[130, 136, 137] however, events were rare across the studies. One study reported no total VTE events, another found no significant difference in total PEs, while the third reported no symptomatic PEs. Total DVT was reported by two studies, one with no events and one with no significant difference between arms. Proximal DVT events also did not occur in one study.

One RCT reported no fatal bleeding events or 30-day mortality. No study reported on adherence.

UFH Versus Combination UFH and LMWH

One RCT compared UFH alone and UFH combined with LMWH.[133] No significant difference was reported in total DVTs. No adverse event or adherence data were reported.

Hip Fracture Surgery

No studies compared single class and combination class interventions after HFx surgery.

Table X12. Results summary: Total hip replacement, single vs. combination class comparisons

Comparison	Outcome	Studies, N	OR, 1 *(Summary OR)*	OR, 2	OR, 3	No Events*
Antiplatelet vs. Antiplatelet+Mechanical	PE, Total	1	0.96 (0.06, 15.5)			
	PE, Fatal	1	No estimate			1 RCT
	DVT, Proximal	1	15.9 (0.90, 281)			
	Bleeding, Fatal	1	No estimate			1 RCT
	Mortality, 30 day or in-hospital	1	0.32 (0.01, 7.85)			
LMWH vs. LMWH+Antiplatelet	VTE, Symptomatic	1	5.80 (0.70, 48.4)			
	PE, Fatal	1	No estimate			1 RCT
	PE, Symptomatic	1	6.73 (0.35, 131)			
	DVT, Symptomatic	1	2.88 (0.30, 27.8)			
	DVT, Proximal	1	1.91 (0.17, 21.2)			
	Bleeding, Major	1	2.89 (0.12, 71.3)			
	Bleeding, Surgical site/joint	1	1.21 (0.32, 4.52)			
	Infection, Wound	1	0.80 (0.34, 1.87)			
LMWH vs. LMWH+DTI	DVT, Total	1	2.36 (0.55, 10.2)			
LMWH vs. LMWH+FXaI	DVT, Total	1	1.27 (0.35, 4.57)			
LMWH vs. LMWH+Mechanical	PE, Total	1	No estimate			1 RCT
	DVT, Total	2	1.80 (0.62, 5.27)	2.25 (0.20, 25.4)		
	DVT, Proximal	2	2.74 (0.75, 10.1)			1 RCT
	Bleeding, Fatal	1	No estimate			1 RCT
	Mortality, 30 day or in-hospital	1	No estimate			1 RCT
Mechanical vs. Antiplatelet+Mechanical	PE, Total	1	0.32 (0.01, 7.87)			
	DVT, Proximal	1	1.25 (0.44, 3.55)			
Mechanical vs. Mechanical+UFH+Antiplatelet	DVT, Total	1	No estimate			1 RCT
	DVT, Symptomatic	1	No estimate			1 RCT
	DVT, Proximal	1	No estimate			1 RCT
	Bleeding, Fatal	1	No estimate			1 RCT
	Mortality, 30 day or in-hospital	1	No estimate			1 RCT
Mechanical vs. Mechanical+VKA	PE, Total	1	No estimate			1 RCT
	DVT, Proximal	1	1.41 (0.47, 4.19)			
UFH vs. UFH+LMWH	DVT, Total	1	0.62 (0.05, 7.00)			

Comparison	Outcome	Studies, N	OR, 1 *(Summary OR)*	OR, 2	OR, 3	No Events*
UFH+Antiplatelet vs. UFH+Antiplatelet+Mechanical	DVT, Total	1	13.7 (0.71, 262)			
	DVT, Symptomatic	1	7.93 (0.39, 162)			
	DVT, Proximal	1	13.7 (0.71, 262)			
	Bleeding, Fatal	1	No estimate			1 RCT
	Mortality, 30 day or in-hospital	1	No estimate			1 RCT

All outcomes for all pairwise comparisons with data from at least one study. If 3 or fewer randomized controlled trials (RCT) with analyzable data (i.e., at least 1 event per study) then each study's odds ratio (OR) is listed in ascending order from left to right. If there were ≥4 analyzable studies, then meta-analysis was conducted and summary OR is reported. These are indicated by italics and by MA (meta-analysis) in the study number column. Statistically significant OR estimates are in bold text. The corresponding studies for each analysis can be found in Appendix F.

Other abbreviations: DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venothromboembolism, Antiplatelet = antiplatelet agent, Mechanical = mechanical devices, LMWH = low molecular weight heparin, DTI = direct thrombin inhibitor, FXaI = factor Xa inhibitor, UFH = unfractionated heparin, VKA = vitamin K antagonist.

* Number of RCTs with no events in both arms.

Table X13. Results summary: Total knee replacement, single vs. combination class comparisons

Comparison	Outcome	Studies, N	OR, 1 *(Summary OR)*	OR, 2	OR, 3	No Events*
Antiplatelet vs. Antiplatelet+Mechanical	DVT, Total	1	**5.45 (2.09, 14.2)**			
	DVT, Proximal	1	13.2 (0.71, 248)			
	Bleeding, Major	1	No estimate			1 RCT
LMWH vs. LMWH+FEI	PE, Total	1	No estimate			1 RCT
	DVT, Total	1	**3.19 (1.48, 6.90)**			
	DVT, Symptomatic	1	No estimate			1 RCT
	DVT, Proximal	1	2.88 (0.29, 28.3)			
	Bleeding, Major	1	No estimate			1 RCT
LMWH vs. LMWH+Mechanical	VTE, Total	1	No estimate			1 RCT
	PE, Total	1	0.99 (0.06, 16.1)			
	PE, Symptomatic	1	No estimate			1 RCT
	DVT, Total	2	1.65 (0.51, 5.28)			1 RCT
	DVT, Proximal	1	No estimate			1 RCT
	Bleeding, Fatal	1	No estimate			1 RCT
	Mortality, 30 day or in-hospital	1	No estimate			1 RCT
UFH vs. UFH+LMWH	DVT, Total	1	0.15 (0.02, 1.31)			

All outcomes for all pairwise comparisons with data from at least one study. If 3 or fewer randomized controlled trials (RCT) with analyzable data (i.e., at least 1 event per study) then each study's odds ratio (OR) is listed in ascending order from left to right. If there were ≥4 analyzable studies, then meta-analysis was conducted and summary OR is reported. These are indicated by italics and by MA (meta-analysis) in the study number column. Statistically significant OR estimates are in bold text. The corresponding studies for each analysis can be found in Appendix F.
Other abbreviations: DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venothromboembolism, Antiplatelet = antiplatelet agent, Mechanical = mechanical devices, LMWH = low molecular weight heparin, FEI = factor VIII inhibitor, UFH = unfractionated heparin.
* Number of RCTs with no events in both arms.

Key Question 5

In patients undergoing major orthopedic surgery, based on network meta-analysis, what are the comparative effects of thromboprophylaxis interventions on deep vein thrombosis and, separately, major bleeding?

5.1 What are the comparative effects of different classes of thromboprophylaxis interventions?

5.2 What are the comparative effects of different individual thromboprophylaxis interventions?

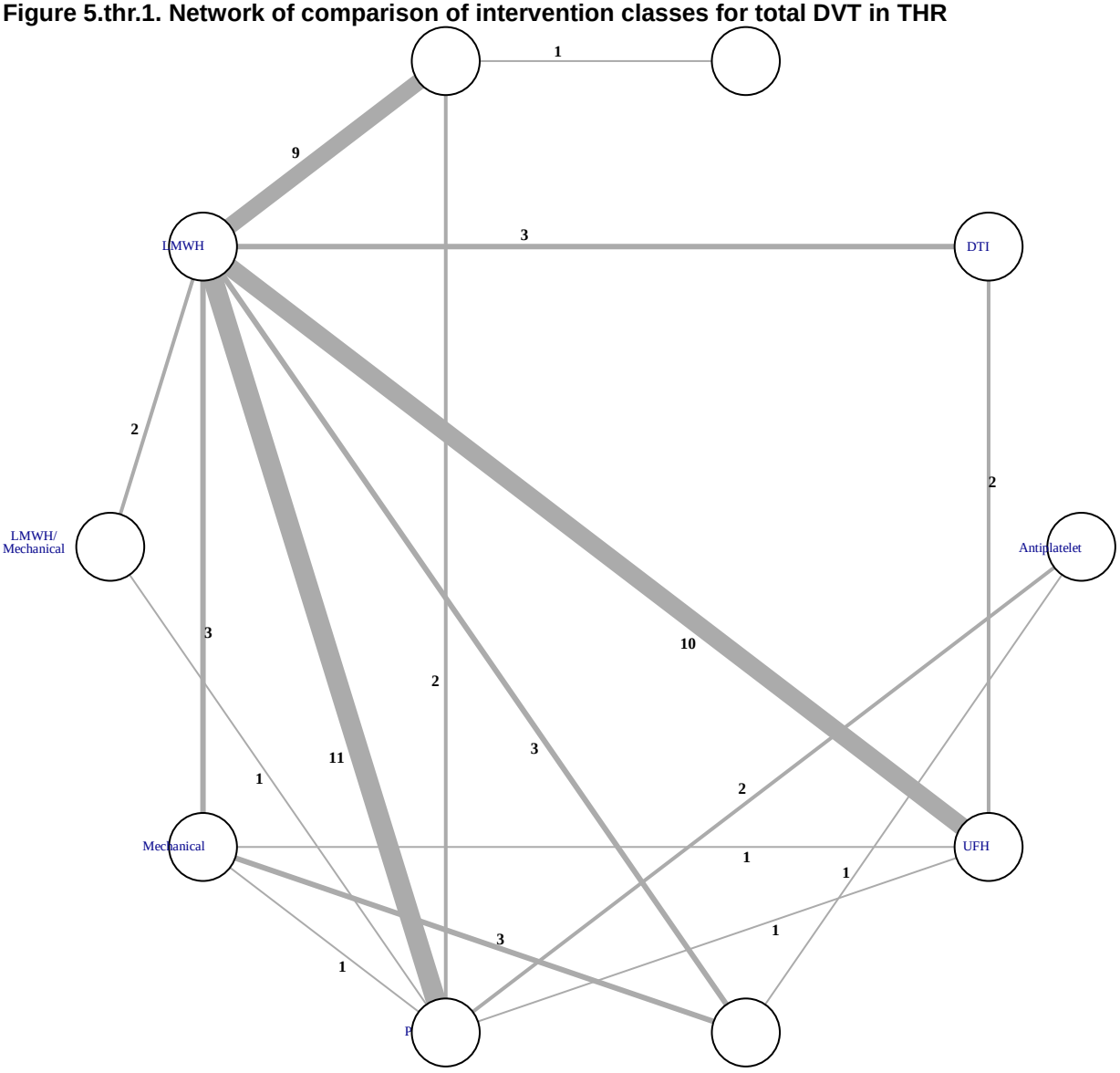
Total Hip Replacement

Deep Vein Thrombosis

Comparison of Classes

There were 50 RCTs that evaluated interventions in at least two classes and reported total DVT after THR.[37, 40-44, 46, 48-50, 52, 54, 55, 57-59, 61-71, 73, 75-81, 114, 130, 131, 138-149] The RCTs compared pairs of intervention classes (47 RCTs) or triplets of intervention classes (3 RCTs). Across this study set, 10 classes were evaluated (antiplatelet drugs, DTI, FEI, FXaI, LMWH, LMWH+mechanical, mechanical, UFH, VKA, placebo). Of the 45 possible pairwise comparisons, 17 are covered by direct study comparisons. **Figure 5.thr.1** illustrates the topology of the network. LMWH was the most common comparator, being directly compared with seven other intervention classes, most frequently with FXaI (9 RCTs), UFH (10 RCTs) and placebo (11 RCTs). Antiplatelet drugs were directly compared with placebo and VKA only; FEI was directly compared with FXaI only.

Figure 5.thr.1. Network of comparison of intervention classes for total DVT in THR



Topology map for network meta-analysis of different classes of thromboprophylaxis interventions for total deep vein thrombosis outcome after total hip replacement. Nodes represent different classes of interventions included in the analysis. Lines between nodes indicate the pairs of intervention classes that were compared directly within trials. The thickness of the lines is proportional to the number of trials directly comparing pairs of interventions, as indicated by the associated number.
Abbreviations: DTI = direct thrombin inhibitor, DVT = deep vein thrombosis, FEI = factor VIII inhibitor, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, THR = total hip replacement, UFH = unfractionated heparin, VKA = vitamin K antagonist.

Appendix Table F7.1 shows the network meta-analysis pairwise results for all combinations of interventions classes. The statistically significant differences between classes are highlighted here.

- **FXaI** had a lower odds of DVT compared with
  - *LMWH* (OR=0.505; 95% CrI 0.336 to 0.765)
  - *UFH* (OR=0.326; 95% CrI 0.188 to 0.562)
  - *VKA* (OR=0.334; 95% CrI 0.182 to 0.634)

- **LMWH** had a lower odds of DVT compared with
    - *UFH* (OR=0.645; 95% CrI 0.444 to 0.921)
- **Mechanical interventions** had lower odds of DVT versus
    - *UFH* (OR=0.538; 95% CrI 0.287 to 0.950)
    - *VKA* (OR=0.550; 95% CrI 0.314 to 0.941)
- The **combination of LMWH plus mechanical intervention** had lower odds of DVT compared with
    - *UFH* (OR=0.214; 95% CrI 0.06 to 0.704)
    - *VKA* (OR=0.218; 95% CrI 0.06 to 0.756).

Summary

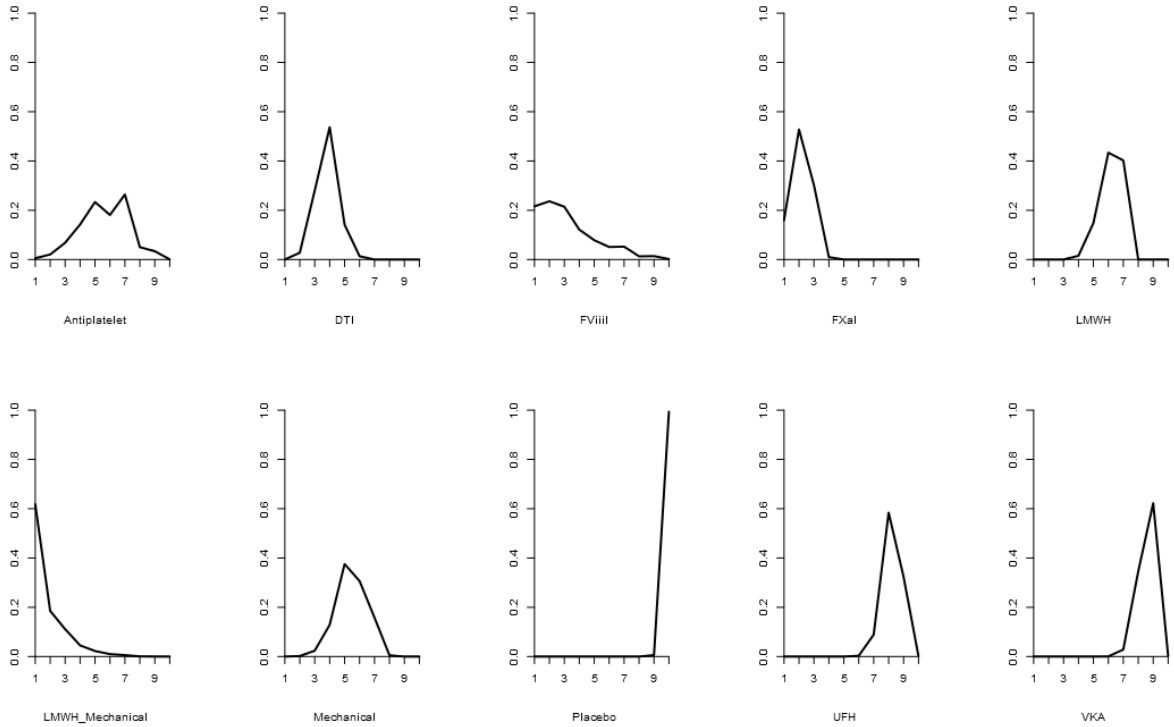
Overall, the combination of LMWH plus mechanical intervention had the highest probability of being among the top three intervention classes (88%) to prevent DVT in patients undergoing THR, followed by FXaI (85%). The interventions likely to be among the bottom three interventions were placebo (>99%), UFH (87%), and VKA (85%) (**Table 5.thr.1**). The distribution of intervention ranks is provided in **Figure 5.thr.2**. However, omitting interventions that are directly linked to two or fewer other interventions with two or fewer RCTs each (antiplatelet drugs, FEI, and combined LMWH and mechanical devices), FXaI is most effective to prevent total DVT, followed by DTI, mechanical devices, LMWH, VKA, and UFH.

Table 5.thr.1. Class ranking: Total hip replacement, intervention class comparisons to prevent DVT

	Top 3 ranks	Bottom 3 ranks
Antiplatelet	21%	12%
DTI	36%	1%
FEI	57%	10%
FXaI	85%	0%
LMWH	0%	3%
LMWH + Mechanical	88%	1%
Mechanical	13%	2%
UFH	0%	87%
VKA	0%	85%
Placebo	0%	100%

Percent likelihood that each class falls within the top 3 or bottom 3 classes in efficacy.
Abbreviations: DTI = direct thrombin inhibitor, DVT = deep vein thrombosis, FEI = factor VIII inhibitor, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, UFH = unfractionated heparin, VKA = vitamin K antagonist.

Figure 5.thr.2. Network meta-analysis ranks of intervention classes to prevent total DVT in THR

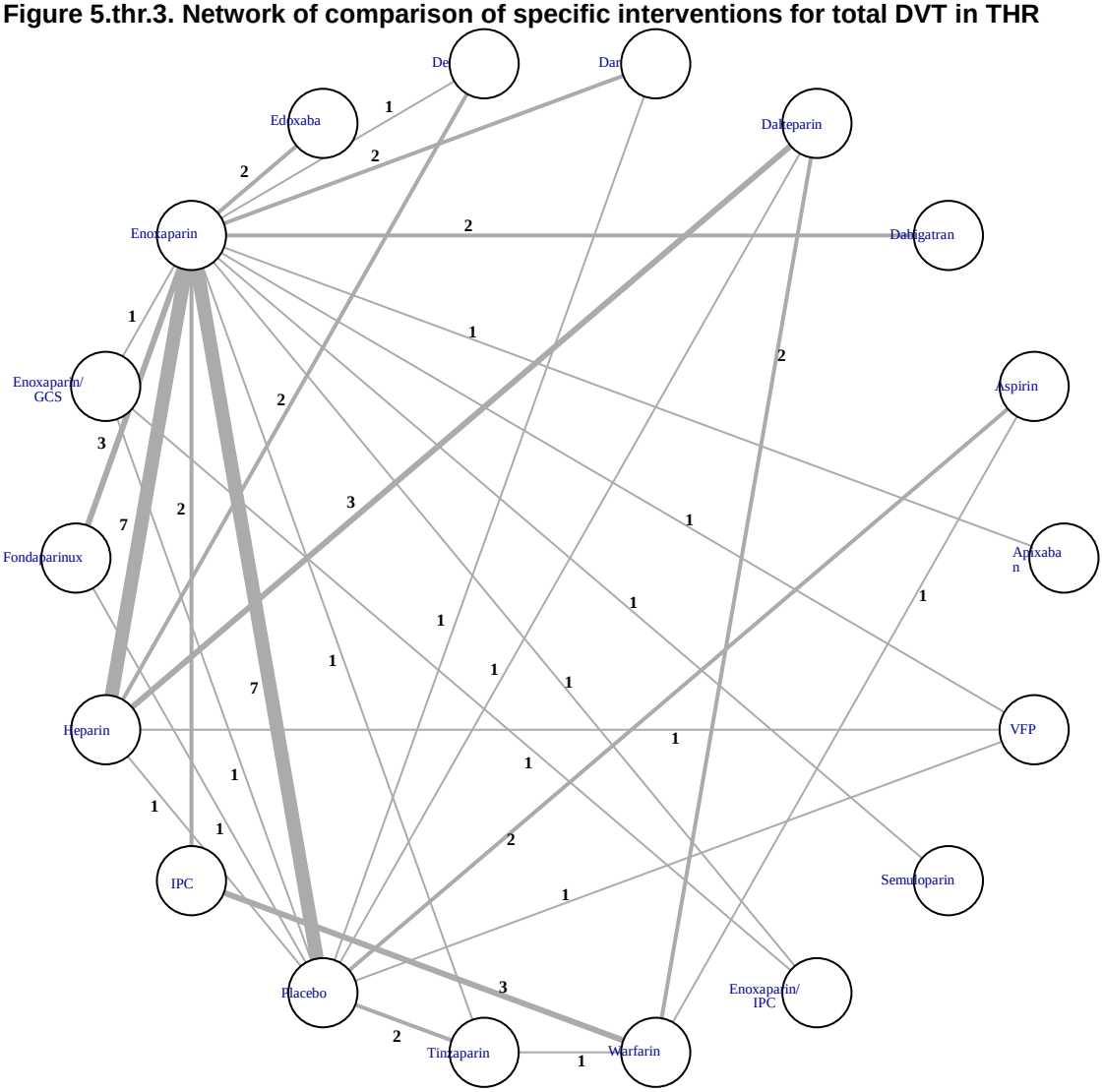


Distribution of probability (y-axis) of treatment rankings (x-axis) by intervention class based on network meta-analysis. Lower ranks indicate lower odds of outcome (greater benefit) with the given intervention compared with others.
Abbreviations: DTI = direct thrombin inhibitor, DVT = deep vein thrombosis, FEI = factor VIII inhibitor, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, THR = total hip replacement, UFH = unfractionated heparin, VKA = vitamin K antagonist.

Comparison of Specific Interventions

In the analysis by drug (or mechanical device), there were 51 RCTs that evaluated at least two interventions and reported total DVT after THR. However, one RCT of TB402 versus rivaroxaban did not connect to the network of evidence and was not included.[42] Hence, there were 50 RCTs in the network meta-analysis.[37, 40, 41, 43, 44, 46, 48-50, 52, 54, 55, 57, 58, 61-71, 73, 75-81, 108, 109, 111, 114, 130, 131, 138-141, 143-149] These RCTs compared pairs of interventions (47 RCTs) or triplets of interventions (3 RCTs). Across this study set, 18 interventions were evaluated (apixaban, aspirin, dabigatran, dalteparin, darexaban, desirudin, edoxaban, enoxaparin, enoxaparin+GCS, enoxaparin+IPC, fondaparinux, heparin, IPC, semuloparin, tinzaparin, VFP, warfarin, placebo). Of the 153 possible pairwise comparisons, 30 are covered by direct study comparisons. **Figure 5.thr.3** illustrates the topology of the network. Enoxaparin was the most common comparator, being directly compared with 14 other interventions; most frequently with heparin (7 RCTs) and placebo (7 RCTs). Dalteparin was directly compared with heparin, warfarin, and placebo only; warfarin was also directly compared with aspirin and IPC; aspirin was also directly compared with placebo.

Figure 5.thr.3. Network of comparison of specific interventions for total DVT in THR



Topology map for network meta-analysis of different interventions of thromboprophylaxis for total deep vein thrombosis outcome after total hip replacement. Nodes represent different interventions included in the analysis. Lines between nodes indicate the pairs of intervention classes that were compared directly within trials. The thickness of the lines is proportional to the number of trials directly comparing pairs of interventions, as indicated by the associated number.
Abbreviations: DVT = deep vein thrombosis, GCS = graduated compression stocking, IPC = intermittent pneumatic compression, THR = total hip replacement, VFP = venous foot pump.

Appendix Table F7.2 shows the network meta-analysis pairwise results for all combinations of interventions. The statistically significant differences between active interventions are highlighted here.

- The combination of **enoxaparin plus IPC** had statistically significant lower odds of DVT compared with 11 active interventions
- **Apixaban** had a lower odds of DVT compared with
    - *dalteparin* (OR=0.312; 95% CrI 0.088 to 0.968)
    - *enoxaparin* (OR=0.308; 95% CrI 0.111 to 0.842)
    - *heparin* (OR=0.211; 95% CrI 0.068 to 0.611)

    - *tinzaparin* (OR=0.199; 95% CrI 0.057 to 0.621)
    - *warfarin* (OR=0.171; 95% CrI 0.049 to 0.557)
- **Desirudin** had a lower odds of DVT compared with
    - *heparin* (OR=0.388; 95% CrI 0.209 to 0.684)
    - *tinzaparin* (OR=0.366; 95% CrI 0.150 to 0.834)
    - *warfarin* (OR=0.311; 95% CrI 0.130 to 0.739)
- **Edoxaban** had a lower odds of DVT compared with
    - *heparin* (OR=0.259; 95% CrI 0.078 to 0.801)
    - *tinzaparin* (OR=0.243; 95% CrI 0.066 to 0.806)
    - *warfarin* (OR=0.211; 95% CrI 0.057 to 0.730)
- **Enoxaparin** had a lower odds of DVT compared with
    - *heparin* (OR=0.684; 95% CrI 0.444 to 0.992)
- The combination of **enoxaparin plus GCS** had a lower odds of DVT compared with
    - *warfarin* (OR=0.236; 95% CrI 0.058 to 0.9)
- **Fondaparinux** had a lower odds of DVT compared with
    - *heparin* (OR=0.488; 95% CrI 0.22 to 0.952)
    - *warfarin* (OR=0.361; 95% CrI 0.152 to 0.899)
- **Semuloparin** had a lower odds of DVT compared with
    - *warfarin* (OR=0.296; 95% CrI 0.091 to 0.898)
- **VFP** had a lower odds of DVT compared with
    - *warfarin* (OR=0.396; 95% CrI 0.148 to 0.963)

Summary

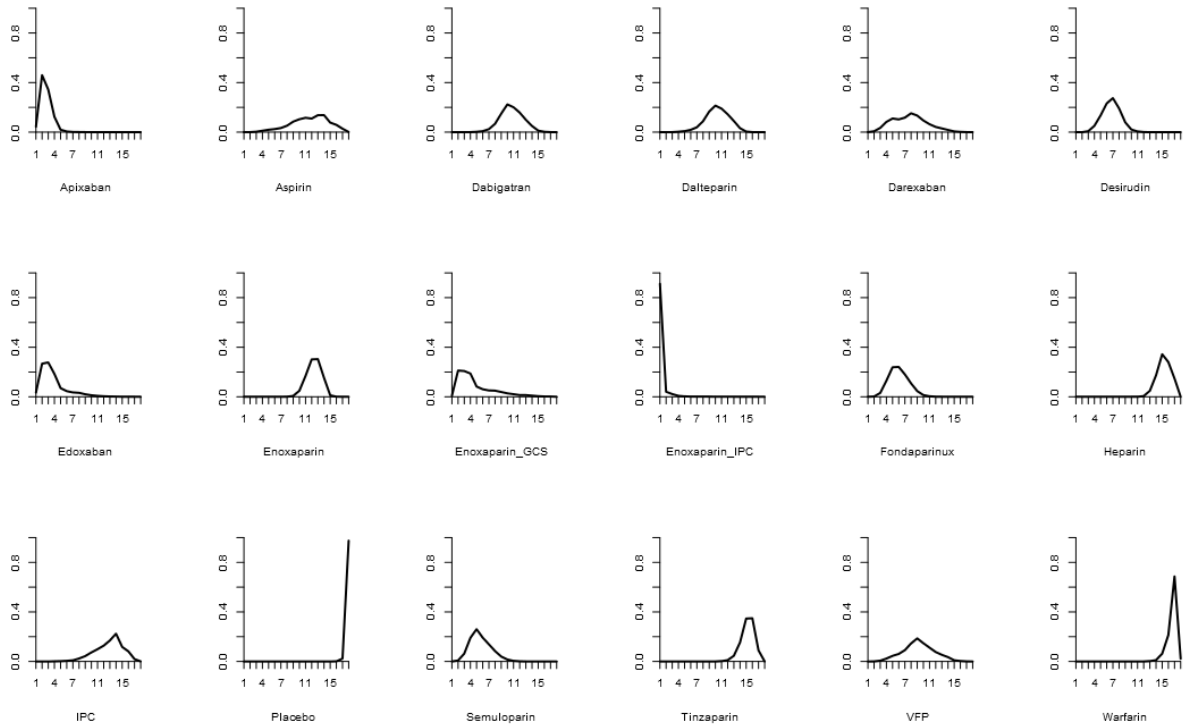
Overall, the combination of enoxaparin plus IPC had the highest probability of being among the top three interventions (96%) to prevent DVT after THR, followed by apixaban (68%). The interventions likely to be among the bottom three interventions were placebo (>99%), warfarin (77%), and tinzaparin (50%) (**Table 5.thr.2**). The distribution of intervention ranks is provided in **Figure 5.thr.4**. However, omitting interventions that are directly linked to two or fewer other interventions with two or fewer RCTs each (most interventions), dalteparin is most effective to prevent total DVTs, followed by enoxaparin, (unfractionated) heparin, and, finally, warfarin.

Table 5.thr.2. Intervention ranking: Total hip replacement, intervention comparisons to prevent DVT

	Top 3 ranks	Bottom 3 ranks
Apixaban	68%	0%
Aspirin	2%	10%
Dabigatran	1%	4%
Dalteparin	0%	3%
Darexaban	7%	3%
Desirudin	10%	0%
Edoxaban	48%	0%
Enoxaparin	0%	0%
Enoxaparin + GCS	40%	2%
Enoxaparin + IPC	96%	0%
Fondaparinux	4%	1%
Heparin	0%	37%
IPC	1%	10%
Semuloparin	20%	1%
Tinzaparin	0%	50%
VFP	4%	1%
Warfarin	0%	77%
Placebo	0%	99%

Percent likelihood that each intervention falls within the top 3 or bottom 3 interventions in efficacy.
Abbreviations: DVT = deep vein thrombosis, GCS = graduated compression stocking, IPC = intermittent pneumatic compression, THR = total hip replacement, VFP = venous foot pump.

Figure 5.thr.4. Network meta-analysis ranks of interventions to prevent total DVT in THR



Distribution of probability (y-axis) of treatment rankings (x-axis) by intervention based on network meta-analysis. Lower ranks indicate lower odds of outcome (greater benefit) with the given intervention compared with others.

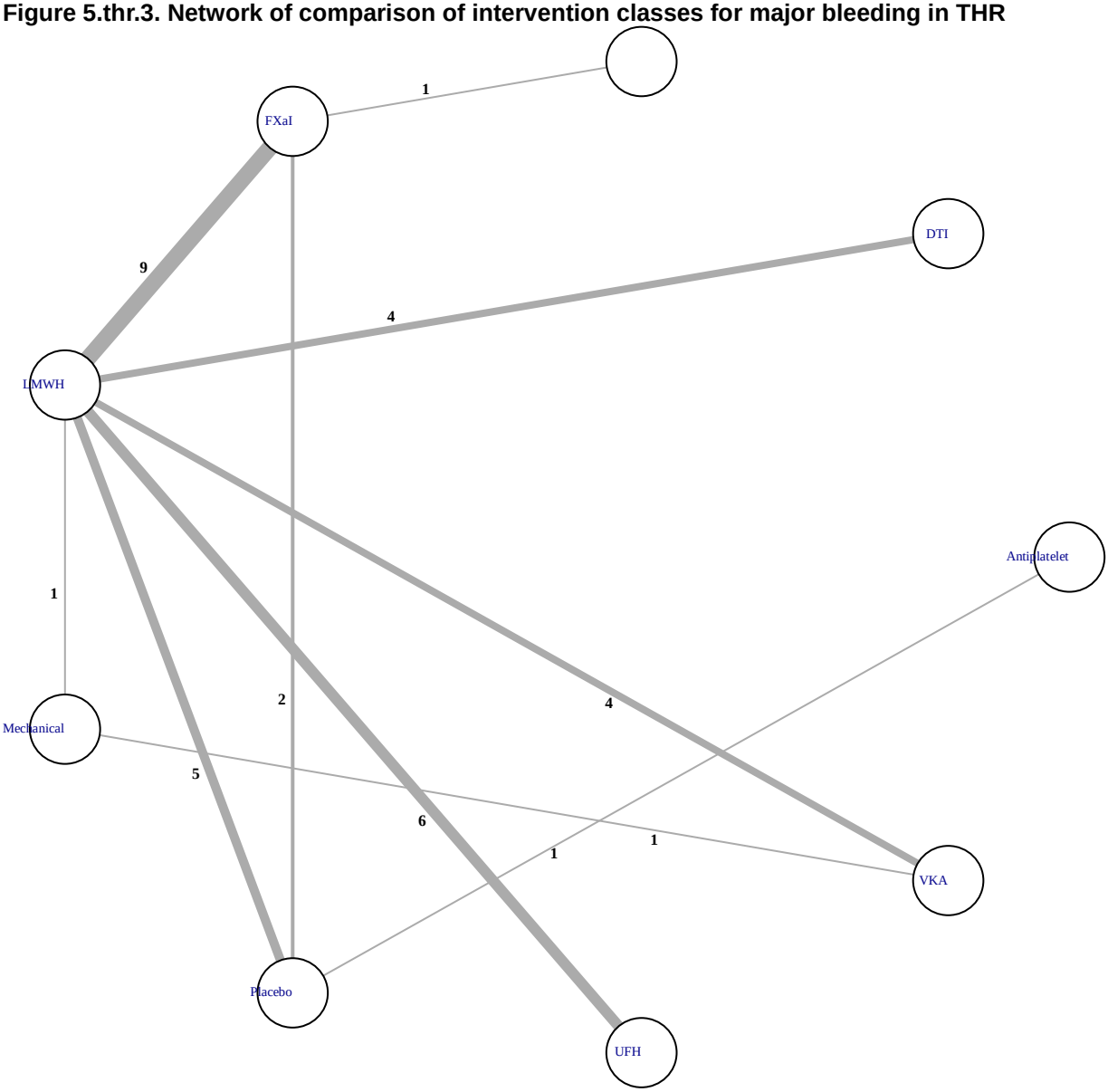
Abbreviations: DVT = deep vein thrombosis, GCS = graduated compression stocking, IPC = intermittent pneumatic compression, THR = total hip replacement, VFP = venous foot pump.

Major Bleeding

Comparison of Classes

There were 30 RCTs that evaluated interventions in at least two classes and reported major bleeding after THR.[42-46, 48-50, 52, 54-58, 62, 64-66, 68, 69, 71, 74-77, 81, 114, 140, 143, 147] The RCTs compared pairs of intervention classes (28 RCTs) or triplets of intervention classes (2 RCTs). Across this study set, 9 classes were evaluated (antiplatelet drugs, DTI, FEI, FXaI, LMWH, mechanical, UFH, VKA, placebo). Of the 36 possible pairwise comparisons, 10 are covered by direct study comparisons. **Figure 5.thr.5** illustrates the topology of the network. LMWH was the most common comparator, being directly compared with six other intervention classes; most frequently with FXaI (9 RCTs), UFH (6 RCTs) and placebo (5 RCTs). Antiplatelet drugs were directly compared with placebo only; FEI was directly compared with FXaI only.

Figure 5.thr.3. Network of comparison of intervention classes for major bleeding in THR



Topology map for network meta-analysis of different classes of thromboprophylaxis interventions for major bleeding outcome after total hip replacement. Nodes represent different classes of interventions included in the analysis. Lines between nodes indicate the pairs of intervention classes that were compared directly within trials. The thickness of the lines is proportional to the number of trials directly comparing pairs of interventions, as indicated by the associated number.
Abbreviations: DTI = direct thrombin inhibitor, FEI = factor VIII inhibitor, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, THR = total hip replacement, UFH = unfractionated heparin, VKA = vitamin K antagonist.

Appendix Table F7.3 shows the network meta-analysis pairwise results for all combinations of interventions. Results for comparisons with antiplatelet drugs, FEI, and mechanical interventions were not estimable (due to the following: there was only one RCT of antiplatelet drugs versus placebo which had zero events; there was only one RCT of FEI versus FXaI which had rare events [5/208 versus 0/208]; there were two RCTs of mechanical interventions which both had zero events). The statistically significant differences between classes are highlighted

here.

- **VKA** had lower odds of major bleeding compared with
  - *DTI* (OR=0.463; 95% CrI 0.266 to 0.802)
  - *FXaI* (OR=0.424; 95% CrI 0.252 to 0.709)
  - *LMWH* (OR=0.59; 95% CrI 0.39 to 0.889)
  - *UFH* (OR=0.268; 95% CrI 0.134 to 0.52)
- **LMWH** had lower odds of major bleeding compared with
  - *FXaI* (OR=0.718; 95% CrI 0.522 to 0.982)
  - *UFH* (OR=0.454; 95% CrI 0.263 to 0.758).

Summary

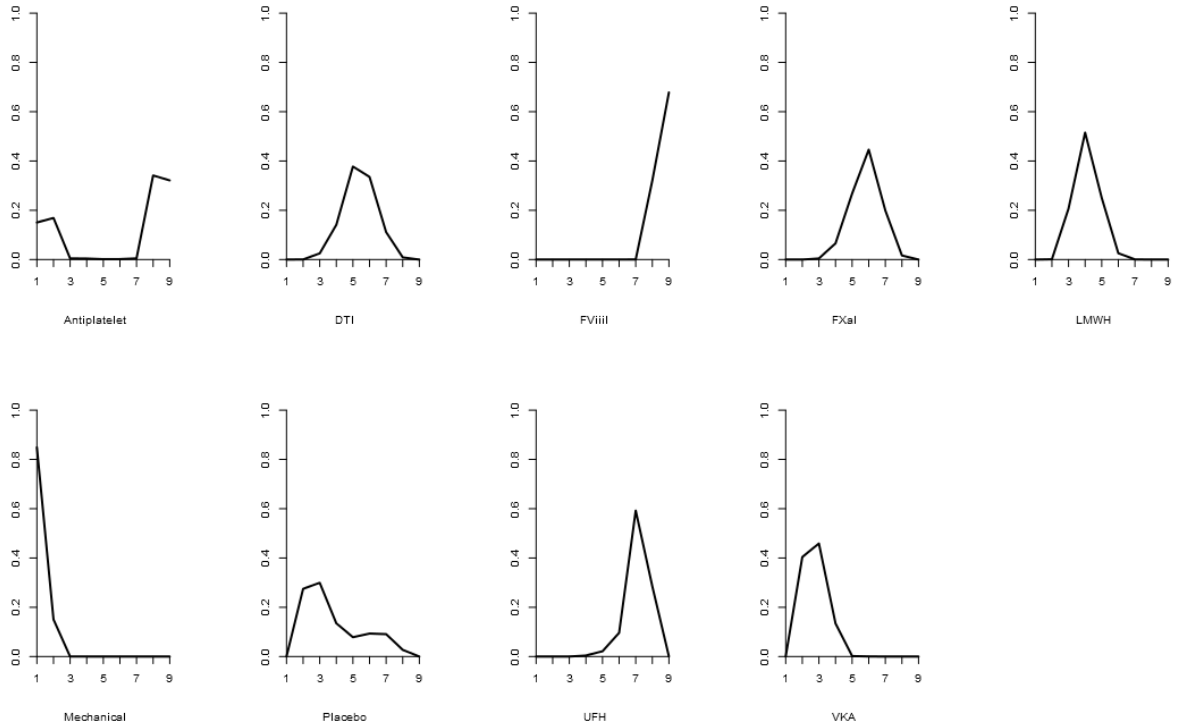
Overall, the mechanical interventions had the highest probability of being among the top three intervention classes (>99%) to avoid major bleeding with thromboprophylaxis after THR, followed by VKA (86%) and placebo (57%). The interventions likely to be among the bottom three interventions were FEI (>99%), UFH (88%), and antiplatelet drugs (67%) (**Table 5.thr.3**). The distribution of intervention ranks is provided in **Figure 5.thr.6**. However, omitting interventions that are directly linked to two or fewer other interventions with two or fewer RCTs each (all classes except LMWH and FXaI—and placebo), LMWH resulted in fewer major bleeding events than FXaI, and placebo was least likely to cause major bleeding.

Table 5.thr.3. Class ranking: Total hip replacement, intervention comparisons to avoid major bleeding

	Top 3 ranks	Bottom 3 ranks
Antiplatelet	32%	67%
DTI	3%	12%
FEI	0%	100%
FXaI	0%	22%
LMWH	21%	0%
Mechanical	100%	0%
UFH	0%	88%
VKA	86%	0%
Placebo	57%	12%

Percent likelihood that each class falls within the top 3 or bottom 3 classes in efficacy.
Abbreviations: DTI = direct thrombin inhibitor, FEI = factor VIII inhibitor, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, THR = total hip replacement, UFH = unfractionated heparin, VKA = vitamin K antagonist.

Figure 5.thr.6. Network meta-analysis ranks of intervention classes to avoid major bleeding in THR

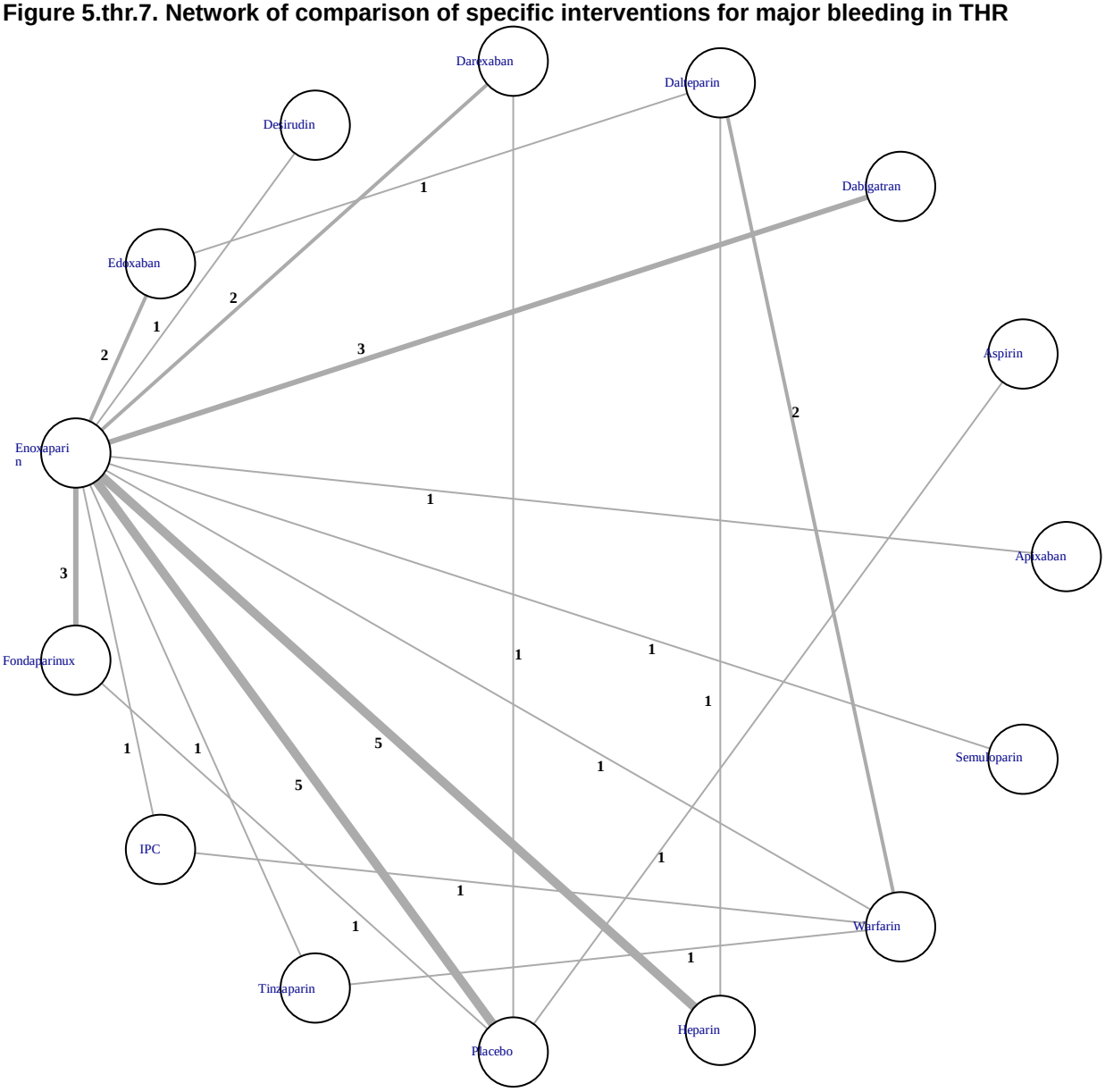


Distribution of probability (y-axis) of treatment rankings (x-axis) by intervention class based on network meta-analysis. Lower ranks indicate lower odds of outcome (greater benefit) with the given intervention compared with others.
Abbreviations: DTI = direct thrombin inhibitor, FEI = factor VIII inhibitor, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, THR = total hip replacement, UFH = unfractionated heparin, VKA = vitamin K antagonist.

Comparison of Specific Interventions

In the analysis by drug (or mechanical device), there were 32 RCTs that evaluated at least two interventions and reported major bleeding after THR. However, one RCT of TB402 versus rivaroxaban did not connect to the network of evidence and was not included.[42] Hence, there were 31 RCTs in the network meta-analysis.[43-46, 48-50, 52, 54-58, 62, 64-66, 68, 69, 71, 74-77, 81, 108, 109, 114, 140, 143, 147] These studies compared pairs of interventions (29 RCTs) or triplets of interventions (2 RCTs). Across this study set, 15 interventions were evaluated (apixaban, aspirin, dabigatran, dalteparin, darexaban, desirudin, edoxaban, enoxaparin, fondaparinux, heparin, IPC, semuloparin, tinzaparin, warfarin, placebo). Of the 105 possible pairwise comparisons, 20 are covered by direct study comparisons. **Figure 5.thr.7** illustrates the topology of the network. Enoxaparin was the most common comparator, being directly compared with 12 other interventions; most frequently with heparin (5 RCTs) and placebo (5 RCTs). Dalteparin was directly compared with heparin, warfarin, and edoxaban only; aspirin was directly compared with placebo only.

Figure 5.thr.7. Network of comparison of specific interventions for major bleeding in THR



Topology map for network meta-analysis of different interventions of thromboprophylaxis for major bleeding outcome after total hip replacement. Nodes represent different interventions included in the analysis. Lines between nodes indicate the pairs of intervention classes that were compared directly within trials. The thickness of the lines is proportional to the number of trials directly comparing pairs of interventions, as indicated by the associated number.
Abbreviations: IPC = intermittent pneumatic compression, THR = total hip replacement.

Appendix Table F7.4 shows the network meta-analysis pairwise results for all combinations of interventions. Results for comparisons with aspirin and IPC were not estimable (due to the following: there was one RCT of aspirin versus placebo which had zero events; there were two RCTs of IPC which both had zero events). The statistically significant differences between active interventions are highlighted here.

- **Semuloparin** had a lower odds of major bleeding compared with
  - *apixaban* (OR=0.218; 95% CrI 0.051 to 0.75)

    - *dabigatran* (OR=0.184; 95% CrI 0.047 to 0.597)
    - *enoxaparin* (OR=0.268; 95% CrI 0.073 to 0.775)
    - *fondaparinux* (OR=0.168; 95% CrI 0.043 to 0.525)
    - *heparin* (OR=0.121; 95% CrI 0.029 to 0.393)
- **Warfarin** had a lower odds of major bleeding compared with
    - *apixaban* (OR=0.302; 95% CrI 0.107 to 0.808)
    - *dabigatran* (OR=0.257; 95% CrI 0.099 to 0.617)
    - *enoxaparin* (OR=0.372; 95% CrI 0.159 to 0.786)
    - *fondaparinux* (OR=0.234; 95% CrI 0.093 to 0.544)
    - *heparin* (OR=0.168; 95% CrI 0.062 to 0.419)
- **Dalteparin** had a lower odds of major bleeding compared with
    - *dabigatran* (OR=0.364; 95% CrI 0.123 to 0.998)
    - *fondaparinux* (OR=0.33; 95% CrI 0.113 to 0.885)
    - *heparin* (OR=0.237; 95% CrI 0.077 to 0.679)
- **Enoxaparin** had a lower odds of major bleeding compared with
    - *fondaparinux* (OR=0.632; 95% CrI 0.426 to 0.929)
    - *heparin* (OR=0.453; 95% CrI 0.262 to 0.761).

Summary

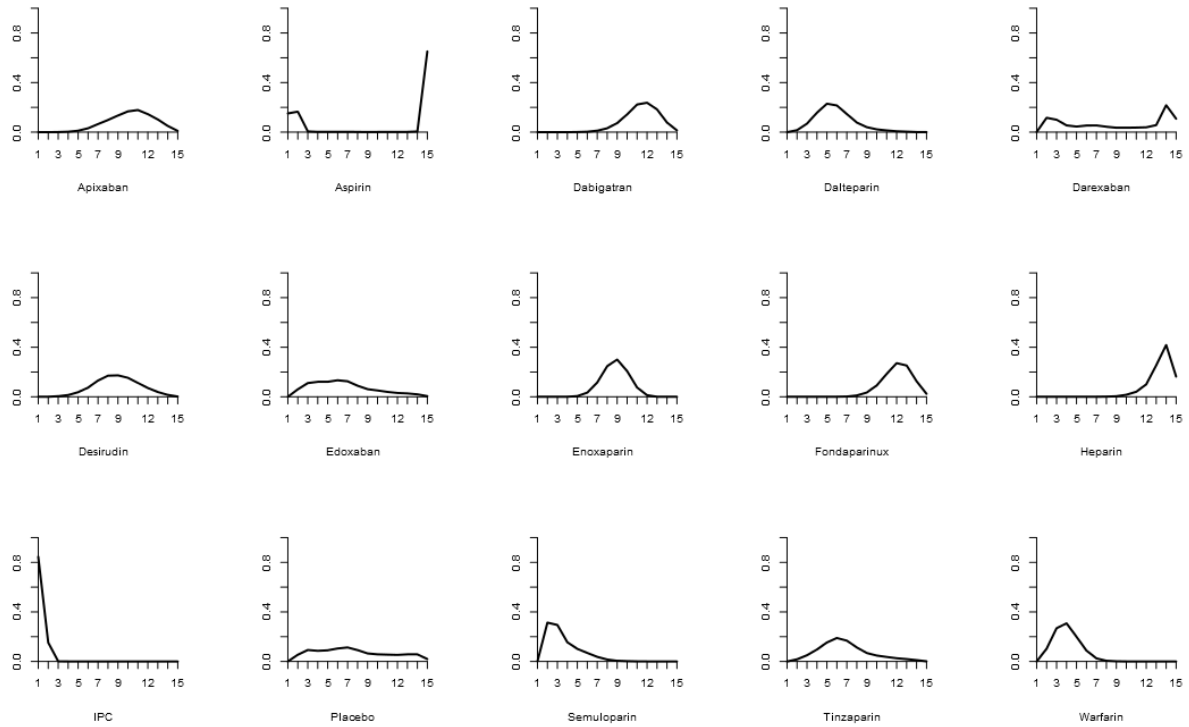
Overall, IPC had the highest probability of being among the top three interventions (>99%) to avoid major bleeding with thromboprophylaxis after THR, followed by semuloparin (61%). The interventions likely to be among the bottom three interventions were heparin (84%) and aspirin (66%) (**Table 5.thr.4**). The distribution of intervention ranks is provided in **Figure 5.thr.8**. However, except for LMWH (and placebo) no intervention was directly compared to more than two other interventions by at least two RCTs each.

Table 5.thr.4. Intervention ranking: Total hip replacement, intervention comparisons to avoid major bleeding

	Top 3 ranks	Bottom 3 ranks
Apixaban	0%	16%
Aspirin	32%	66%
Dabigatran	0%	28%
Dalteparin	8%	1%
Darexaban	22%	38%
Desirudin	1%	6%
Edoxaban	17%	5%
Enoxaparin	0%	0%
Fondaparinux	0%	40%
Heparin	0%	84%
IPC	100%	0%
Semuloparin	61%	0%
Tinzaparin	7%	3%
Warfarin	37%	0%
Placebo	15%	13%

Percent likelihood that each intervention falls within the top 3 or bottom 3 interventions in efficacy.
Abbreviations: IPC = intermittent pneumatic compression, THR = total hip replacement.

Figure 5.thr.8. Network meta-analysis ranks of interventions to avoid major bleeding in THR



Distribution of probability (y-axis) of treatment rankings (x-axis) by intervention based on network meta-analysis. Lower ranks indicate lower odds of outcome (greater benefit) with the given intervention compared with others.
Abbreviations: IPC = intermittent pneumatic compression, THR = total hip replacement.

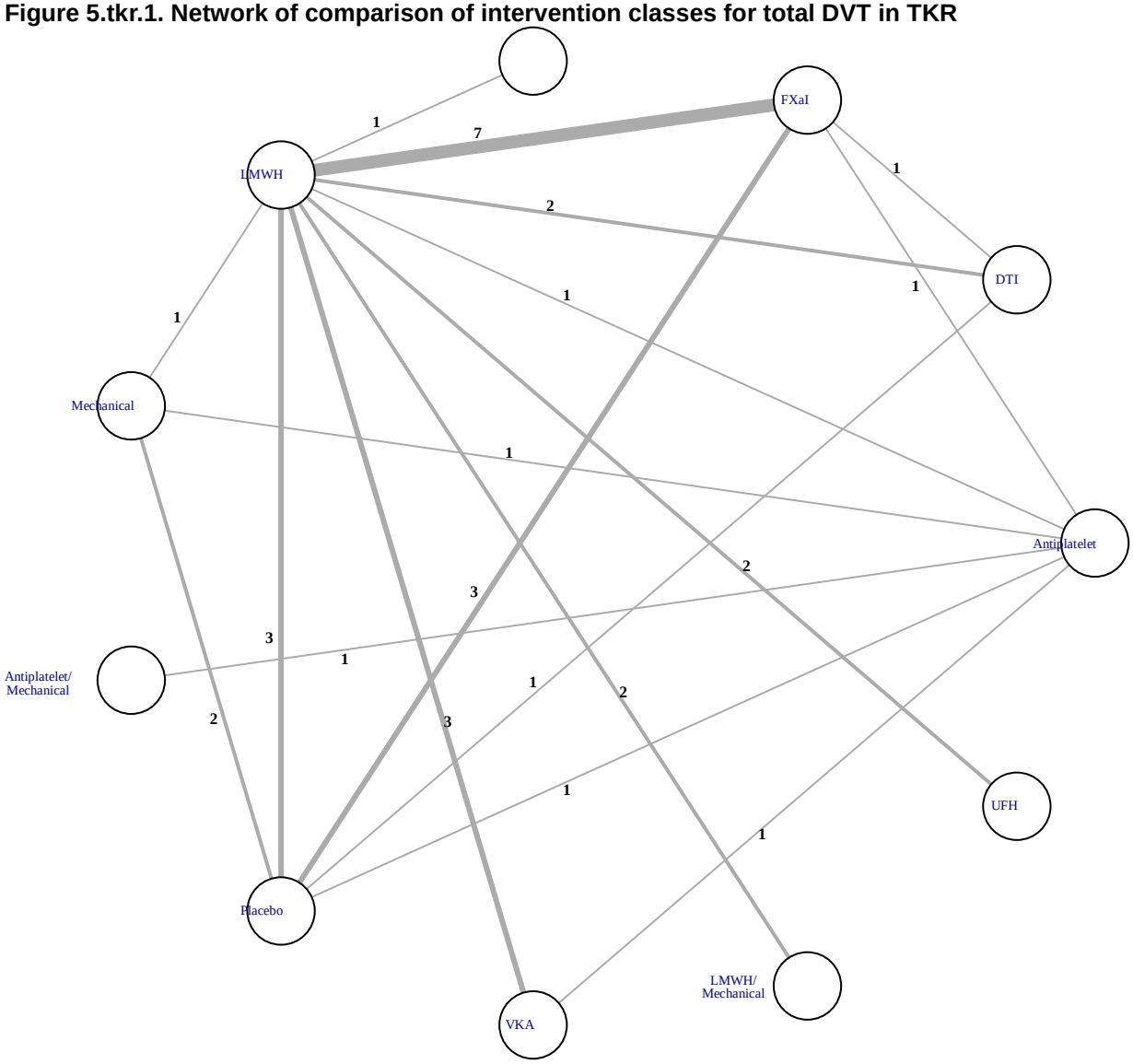
Total Knee Replacement

Deep Vein Thrombosis

Comparison of Classes

There were 28 RCTs that evaluated interventions in at least two classes and reported total DVT after TKR.[37, 46, 49, 60, 75, 82-84, 89-92, 95-100, 114, 118, 130, 134, 137, 150-154] The RCTs compared pairs of intervention classes (25 RCTs) or triplets of intervention classes (3 RCTs). Across this study set, 11 classes were evaluated (antiplatelet drugs, antiplatelet drugs + mechanical, DTI, FXaI, FXIi, LMWH, LMWH+mechanical, Mechanical, UFH, VKA, placebo). Of the 55 possible pairwise comparisons, 18 are covered by direct study comparisons. **Figure 5.tkr.1** illustrates the topology of the network. LMWH was the most common comparator, being directly compared with nine other intervention classes; most frequently with FXaI (7 RCTs). The combination of antiplatelet drugs plus mechanical was directly compared with antiplatelet drugs only.

Figure 5.tkr.1. Network of comparison of intervention classes for total DVT in TKR



Topology map for network meta-analysis of different classes of thromboprophylaxis interventions for total deep vein thrombosis outcome after total knee replacement. Nodes represent different classes of interventions included in the analysis. Lines between nodes indicate the pairs of intervention classes that were compared directly within trials. The thickness of the lines is proportional to the number of trials directly comparing pairs of interventions, as indicated by the associated number.
Abbreviations: DTI = direct thrombin inhibitor, DVT = deep vein thrombosis, FXaI = factor Xa inhibitor, FXIi = factor XI inhibitor, LMWH = low molecular weight heparin, TKR = total knee replacement, UFH = unfractionated heparin, VKA = vitamin K antagonist.

Appendix Table F7.5 shows the network meta-analysis pairwise results for for all combinations of interventions classes. The statistically significant differences between classes are highlighted here.

- FXaI had a lower odds of DVT compared with antiplatelet drugs (OR=0.253; 95% CrI 0.16 to 0.391), LMWH (OR=0.482; 95% CrI 0.404 to 0.574), mechanical (OR=0.466; 95% CrI 0.291 to 0.75), UFH (OR=0.321; 95% CrI 0.216 to 0.475), and VKA (OR=0.272; 95% CrI 0.208 to 0.357).

- The combination of antiplatelet drugs plus mechanical had a lower odds of DVT compared with antiplatelet drugs (OR=0.177; 95% CrI 0.064 to 0.445), LMWH (OR=0.336; 95% CrI 0.112 to 0.94), mechanical (OR=0.326; 95% CrI 0.104 to 0.949), UFH (OR=0.224; 95% CrI 0.07 to 0.656), and VKA (OR=0.19; 95% CrI 0.064 to 0.524).
- DTI had a lower odds of DVT compared with antiplatelet drugs (OR=0.295; 95% CrI 0.156 to 0.552), LMWH (OR=0.562; 95% CrI 0.351 to 0.899), UFH (OR=0.376; 95% CrI 0.207 to 0.67), and VKA (OR=0.317; 95% CrI 0.19 to 0.532).
- LMWH had a lower odds of DVT compared with antiplatelet drugs (OR=0.525; 95% CrI 0.337 to 0.793), UFH (OR=0.668; 95% CrI 0.468 to 0.946), and VKA (OR=0.565; 95% CrI 0.459 to 0.694).
- FXIi had a lower odds of DVT compared with antiplatelet drugs (OR=0.41; 95% CrI 0.192 to 0.885) and VKA (OR=0.441; 95% CrI 0.227 to 0.866).
- Mechanical interventions had lower odds of DVT versus antiplatelet drugs (OR=0.542; 95% CrI 0.323 to 0.908) and VKA (OR=0.585; 95% CrI 0.36 to 0.941).

Summary

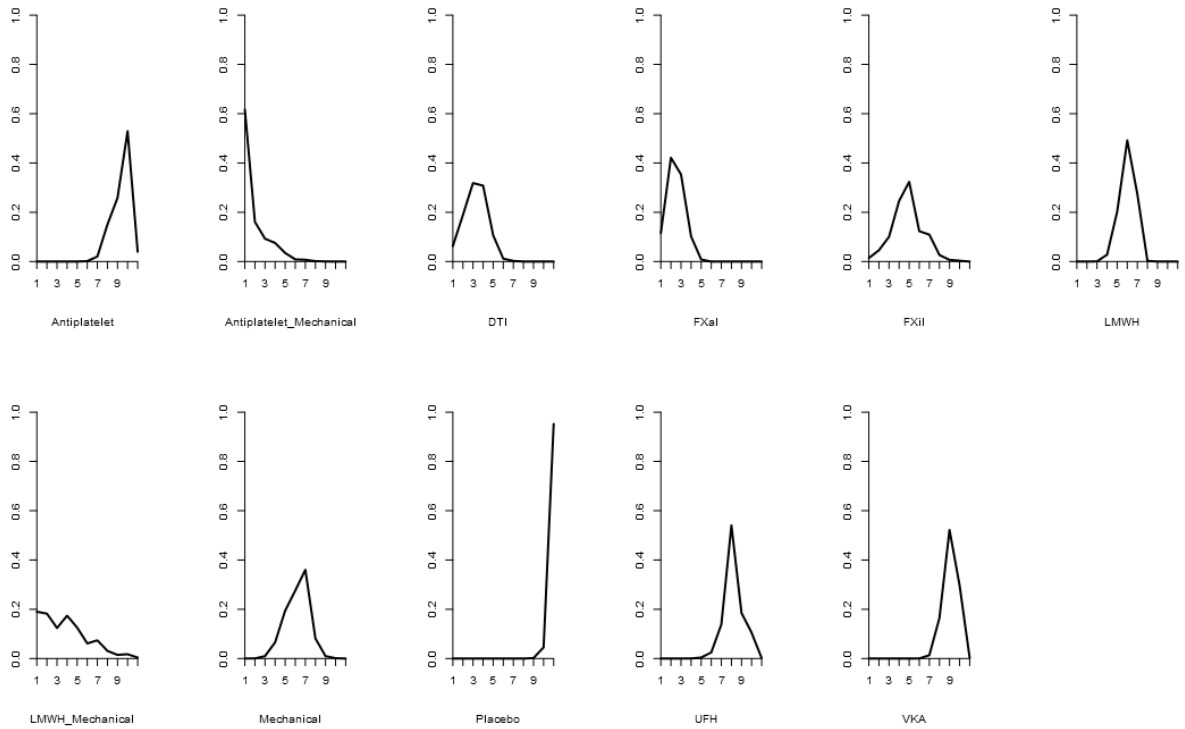
Overall, FXaI had the highest probability of being among the top three intervention classes (89%) to prevent DVT after TKR, followed closely by the combination of antiplatelet drugs plus mechanical (87%), then DTI (57%). The interventions likely to be among the bottom three interventions were placebo (>99%), antiplatelet drugs (83%), and VKA (82%) (**Table 5.tkr.1**). The distribution of intervention ranks is provided in **Figure 5.tkr.2**. However, except for enoxaparin (and placebo) no intervention was directly compared to more than two other interventions by at least two RCTs each.

Table 5.tkr.1. Class ranking: Total knee replacement, intervention class comparisons to prevent DVT

	Top 3 ranks	Bottom 3 ranks
Antiplatelet	0%	83%
Antiplatelet + Mechanical	87%	0%
DTI	57%	0%
FXaI	89%	0%
FXIi	16%	1%
LMWH	0%	0%
LMWH + Mechanical	50%	4%
Mechanical	1%	1%
UFH	0%	29%
VKA	0%	82%
Placebo	0%	100%

Percent likelihood that each class falls within the top 3 or bottom 3 classes in efficacy.
Abbreviations: DTI = direct thrombin inhibitor, DVT = deep vein thrombosis, FXaI = factor Xa inhibitor, FXIi = factor XI inhibitor, LMWH = low molecular weight heparin, TKR = total knee replacement, UFH = unfractionated heparin, VKA = vitamin K antagonist.

Figure 5.tkr.2. Network meta-analysis ranks of intervention classes to prevent total DVT in TKR

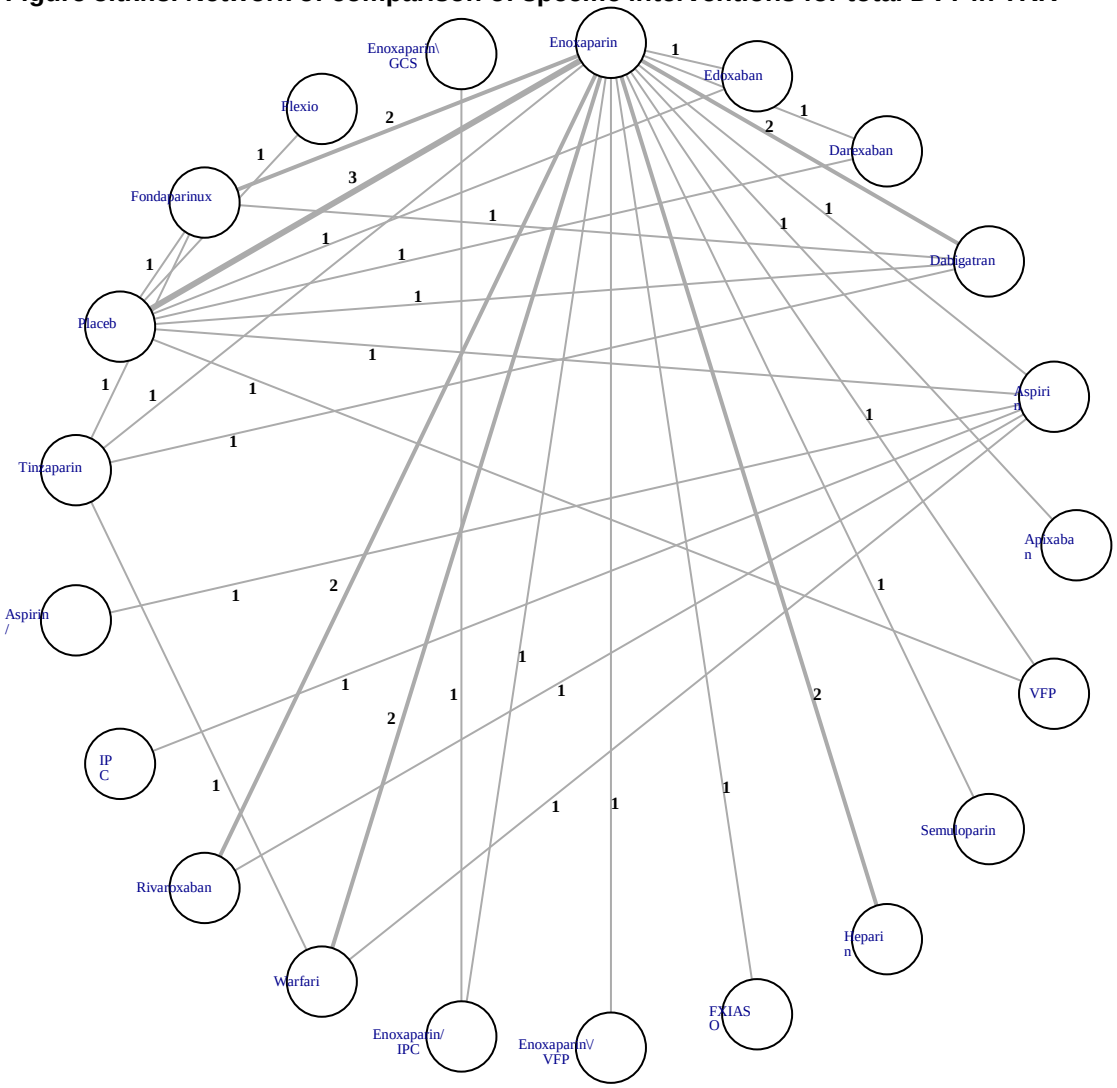


Distribution of probability (y-axis) of treatment rankings (x-axis) by intervention class based on network meta-analysis. Lower ranks indicate lower odds of outcome (greater benefit) with the given intervention compared with others.
Abbreviations: DTI = direct thrombin inhibitor, DVT = deep vein thrombosis, FXaI = factor Xa inhibitor, FXIi = factor XI inhibitor, LMWH = low molecular weight heparin, TKR = total knee replacement, UFH = unfractionated heparin, VKA = vitamin K antagonist.

Comparison of Specific Interventions

In the analysis by drug (or mechanical device), there were 30 RCTs that evaluated at least two interventions and reported total DVT after TKR.[37, 46, 49, 60, 75, 82-84, 89-92, 95-100, 108, 111, 114, 118, 130, 134, 137, 150-154] The RCTs compared pairs of interventions (27 RCTs), triplets of interventions (2 RCTs), or quadruplets of interventions (1 RCT). Across this study set, 21 interventions were evaluated (apixaban, aspirin, aspirin+VFP, dabigatran, darexaban, edoxaban, enoxaparin, enoxaparin+GCS, enoxaparin+IPC, enoxaparin+VFP, flexion, fondaparinux, FXIASO, heparin, IPC, rivaroxaban, semuloparin, tinzaparin, VFP, warfarin, placebo). Of the 210 possible pairwise comparisons, 32 are covered by direct study comparisons. **Figure 5.tkr.3** illustrates the topology of the network. Enoxaparin was the most common comparator, being directly compared with 16 other interventions. Flexion was directly compared with placebo only; enoxaparin+GCS was directly compared with enoxaparin+IPC only; IPC and aspirin+VFP were directly compared with aspirin only.

Figure 5.tkr.3. Network of comparison of specific interventions for total DVT in TKR



Topology map for network meta-analysis of different interventions of thromboprophylaxis for total deep vein thrombosis outcome after total knee replacement. Nodes represent different interventions included in the analysis. Lines between nodes indicate the pairs of intervention classes that were compared directly within trials. The thickness of the lines is proportional to the number of trials directly comparing pairs of interventions, as indicated by the associated number.
Abbreviations: DVT = deep vein thrombosis, FXIASO = factor XI antisense oligonuclide, GCS = graduated compression stocking, IPC = intermittent pneumatic compression, TKR = total hip replacement, VFP = venous foot pump.

Appendix Table F7.6 shows the network meta-analysis pairwise results for all combinations of interventions. Results for the combination of enoxaparin plus GCS, the combination of enoxaparin plus IPC, and flexion devices were not estimable (due to the following: there was one RCT of enoxaparin plus GCS versus enoxaparin plus IPC which had small sample size and rare events [14/35 versus 0/35]; there was one RCT of flexion device versus placebo which had zero events). The statistically significant differences between active interventions are highlighted here.

- **Rivaroxaban** had a lower odds of DVT compared with 8 active interventions.

- **Apixaban** had a lower odds of DVT compared with 7 active interventions
- **Fondaparinux** had a lower odds of DVT compared with 7 active interventions
- The combination of **aspirin plus VFP** had a lower odds of DVT compared with 6 active interventions
- **Dabigatran** had a lower odds of DVT compared with 6 active interventions
- **Edoxaban** had a lower odds of DVT compared with
    - *aspirin* (OR=0.295; 95% CrI 0.15 to 0.585)
    - *heparin* (OR=0.317; 95% CrI 0.177 to 0.559)
    - *tinzaparin* (OR=0.376; 95% CrI 0.2 to 0.697)
    - *VFP* (OR=0.395; 95% CrI 0.2 to 0.774)
    - *warfarin* (OR=0.252, 95% CrI 0.149 to 0.424)
- **Darexaban** had a lower odds of DVT compared with
    - *aspirin* (OR=0.34; 95% CrI 0.134 to 0.837)
    - *heparin* (OR=0.356; 95% CrI 0.152 to 0.836)
    - *warfarin* (OR=0.29; 95% CrI 0.125 to 0.642)
- **Semuloparin** had a lower odds of DVT compared with
    - *aspirin* (OR=0.515; 95% CrI 0.289 to 0.922)
    - *heparin* (OR=0.554; 95% CrI 0.347 to 0.875)
    - *warfarin* (OR=0.441; 95% CrI 0.295 to 0.653)
- **Enoxaparin** had a lower odds of DVT compared with
    - *heparin* (OR=0.666; 95% CrI 0.469 to 0.946)
    - *warfarin* (OR=0.53; 95% CrI 0.407 to 0.688)
- **IPC** had a lower odds of DVT compared with
    - *aspirin* (OR=0.392; 95% CrI 0.181 to 0.815)
    - *warfarin* (OR=0.333; 95% CrI 0.137 to 0.81)
- **FXIASO** had a lower odds of DVT compared with
    - *warfarin* (OR=0.415; 95% CrI 0.211 to 0.82)
- **Tinzaparin** had a lower odds of DVT compared with
    - *warfarin* (OR=0.67; 95% CrI 0.475 to 0.942)

Summary

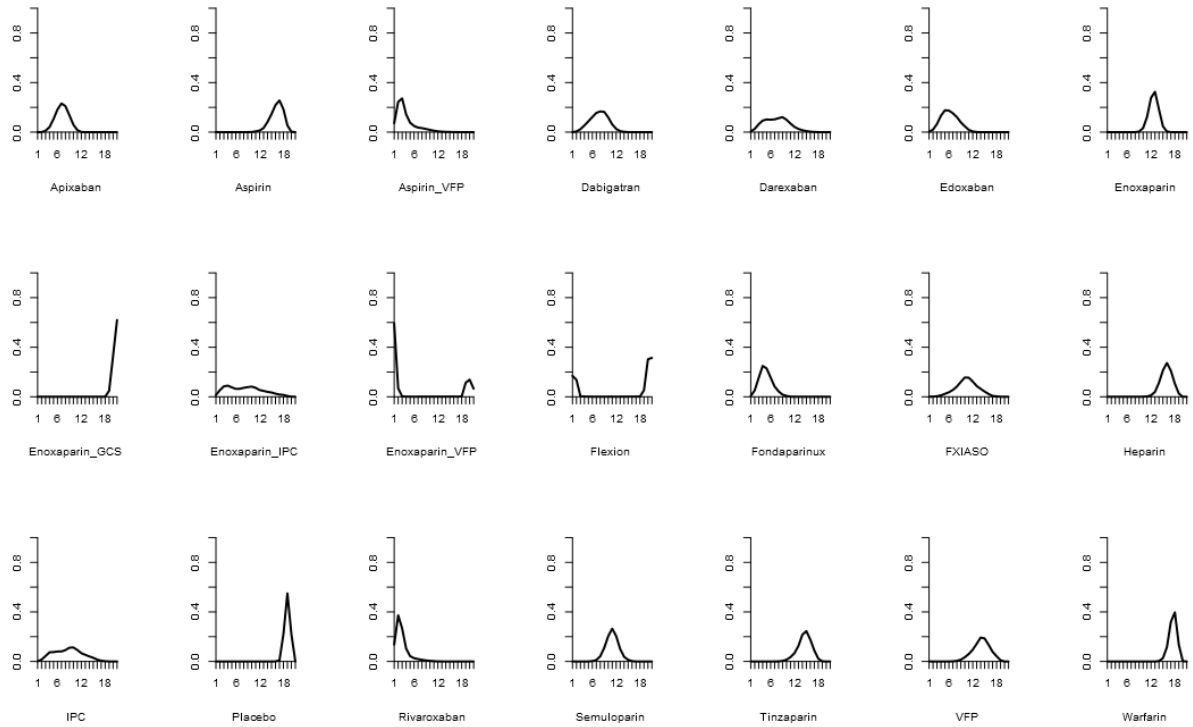
Overall, rivaroxaban had the highest probability of being among the top three interventions to prevent DVT after TKR, followed by the combination of enoxaparin plus VFP (66%) and the combination of aspirin plus VFP (59%). The interventions likely to be among the bottom three interventions were the combination of enoxaparin plus GCS (>99%), placebo (77%), and flexion device (67%) (**Table 5.tkr.2**). The distribution of intervention ranks is provided in **Figure 5.tkr.4**. However, except for enoxaparin (and placebo) no intervention was directly compared to more than two other interventions by at least two RCTs each.

Table 5.tkr.2. Intervention ranking: Total knee replacement, intervention class comparisons to prevent DVT

	Top 3 ranks	Bottom 3 ranks
Apixaban	1%	0%
Aspirin	0%	6%
Aspirin + VFP	59%	0%
Dabigatran	3%	0%
Darexaban	10%	0%
Edoxaban	9%	0%
Enoxaparin	0%	0%
Enoxaparin + GCS	0%	100%
Enoxaparin + IPC	15%	1%
Enoxaparin + VFP	66%	32%
Flexion	31%	67%
Fondaparinux	21%	0%
FXIASO	1%	0%
Heparin	0%	3%
IPC	6%	0%
Rivaroxaban	77%	0%
Semuloparin	0%	0%
Tinzaparin	0%	0%
VFP	0%	1%
Warfarin	0%	14%
Placebo	0%	77%

Percent likelihood that each intervention falls within the top 3 or bottom 3 interventions in efficacy.
Abbreviations: DVT = deep vein thrombosis, FXIASO = factor XI antisense oligonuclide, GCS = graduated compression stocking, IPC = intermittent pneumatic compression, TKR = total hip replacement, VFP = venous foot pump.

Figure 5.tkr.4. Network meta-analysis ranks of interventions to prevent total DVT in TKR



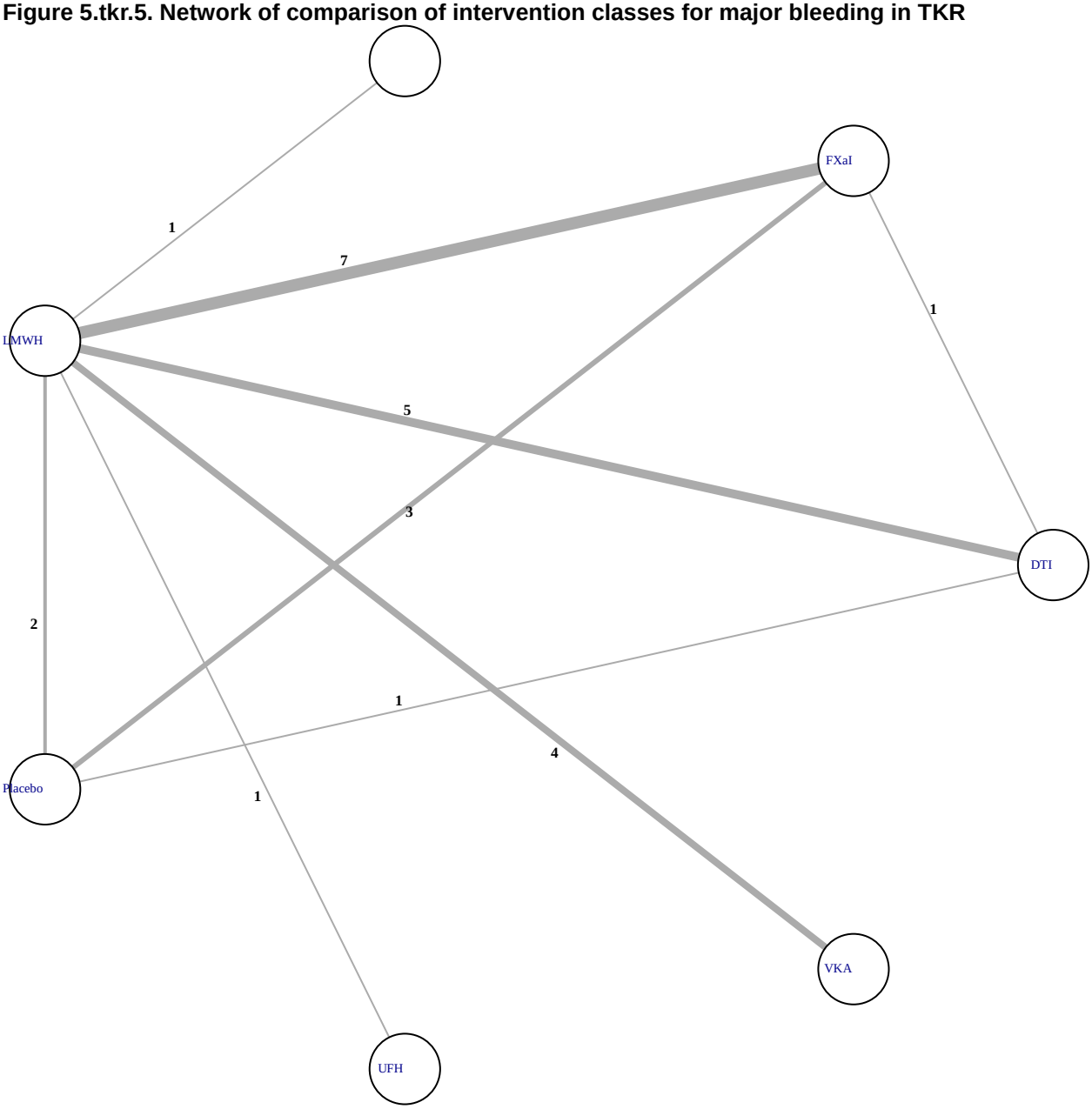
Distribution of probability (y-axis) of treatment rankings (x-axis) by intervention based on network meta-analysis. Lower ranks indicate lower odds of outcome (greater benefit) with the given intervention compared with others.
Abbreviations: DVT = deep vein thrombosis, FXIASO = factor XI antisense oligonuclide, GCS = graduated compression stocking, IPC = intermittent pneumatic compression, TKR = total hip replacement, VFP = venous foot pump.

Major Bleeding

Comparison of Classes

There were 22 RCTs that evaluated interventions in at least two classes and reported major bleeding after TKR. However, one RCT of antiplatelet drugs versus the combination of antiplatelet drugs plus mechanical did not connect to the network of evidence and was not included.[134] Hence, there were 21 RCTs in the network meta-analysis.[46, 49, 60, 75, 84-87, 90-95, 98-101, 114, 118, 152] These RCTs compared pairs of intervention classes (19 RCTs) or triplets of intervention classes (2 RCTs). Across this study set, 7 classes were evaluated (DTI, FXaI, FXIi, LMWH, UFH, VKA, placebo). Of the 21 possible pairwise comparisons, 9 are covered by direct study comparisons. **Figure 5.tkr.5** illustrates the topology of the network. LMWH was the most common comparator, being directly compared with each of the six other intervention classes; most frequently with FXaI (7 RCTs), DTI (5 RCTs), and VKA (4 RCTs).

Figure 5.tkr.5. Network of comparison of intervention classes for major bleeding in TKR



Topology map for network meta-analysis of different classes of thromboprophylaxis interventions for major bleeding outcome after total knee replacement. Nodes represent different classes of interventions included in the analysis. Lines between nodes indicate the pairs of intervention classes that were compared directly within trials. The thickness of the lines is proportional to the number of trials directly comparing pairs of interventions, as indicated by the associated number.
Abbreviations: DTI = direct thrombin inhibitor, FXaI = factor Xa inhibitor, FXIi = factor XI inhibitor, LMWH = low molecular weight heparin, TKR = total knee replacement, UFH = unfractionated heparin, VKA = vitamin K antagonist.

Appendix Table F7.7 shows the network meta-analysis pairwise results for for all combinations of interventions classes. Results for comparisons versus FXIi were not estimable (due to the following: there was one RCT of FXIi versus enoxaparin which had zero events). The statistically significant differences between classes are highlighted here.

- **VKA** had a lower odds of major bleeding compared with
    - *FXaI* (OR=0.359; 95% CrI 0.145 to 0.864)
    - *LMWH* (OR=0.497; 95% CrI 0.243 to 0.959)

Summary

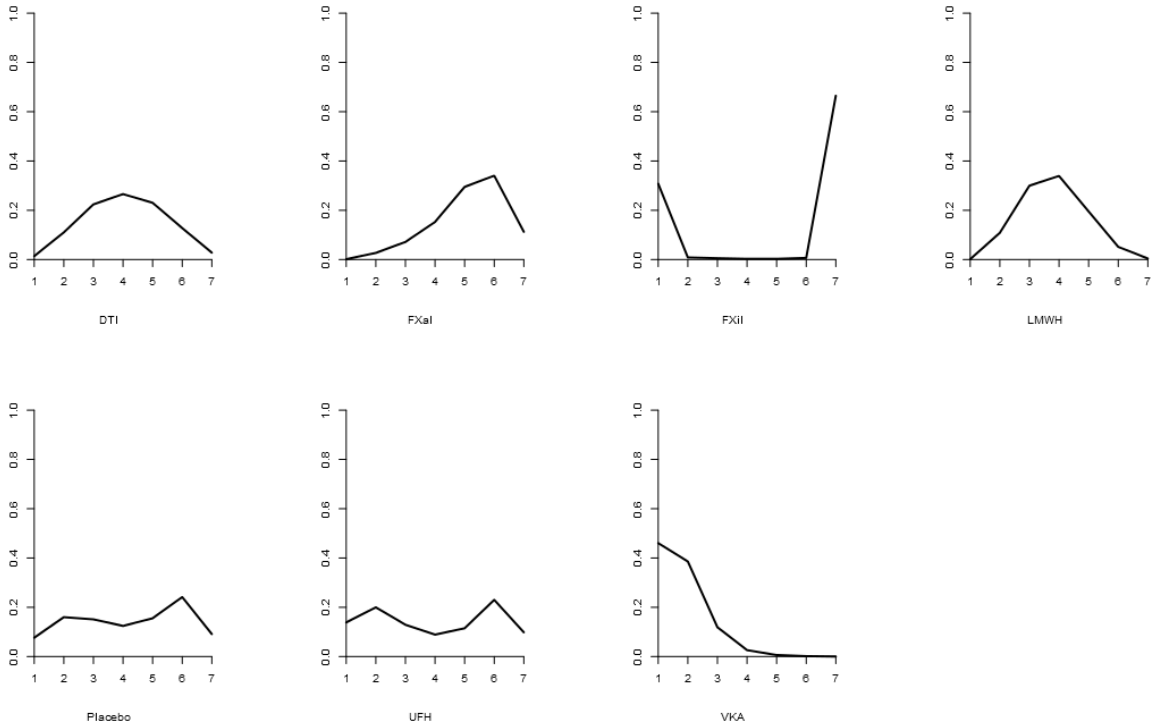
Overall, VKA had the highest probability of being among the top three intervention classes (97%) to avoid major bleeding with thromboprophylaxis after TKR. Notably, though the mechanical devices RCTs did not provide major bleeding data. The interventions likely to be among the bottom three interventions were FXaI (75%) and FXIi (67%) (**Table 5.tkr.3**). The distribution of intervention ranks is provided in **Figure 5.tkr.6**. However, except for LMWH (and placebo) no intervention was directly compared to more than two other interventions by at least two RCTs each.

Table 5.tkr.3. Class ranking: Total knee replacement, intervention class comparisons to avoid major bleeding

	Top 3 ranks	Bottom 3 ranks
DTI	35%	39%
FXaI	10%	75%
FXIi	32%	67%
LMWH	41%	25%
UFH	47%	44%
VKA	97%	1%
Placebo	39%	49%

Percent likelihood that each class falls within the top 3 or bottom 3 classes in efficacy.
Abbreviations: DTI = direct thrombin inhibitor, DVT = deep vein thrombosis, FXaI = factor Xa inhibitor, FXIi = factor XI inhibitor, LMWH = low molecular weight heparin, TKR = total knee replacement, UFH = unfractionated heparin, VKA = vitamin K antagonist.

Figure 5.tkr.6. Network meta-analysis ranks of intervention classes to avoid major bleeding in TKR

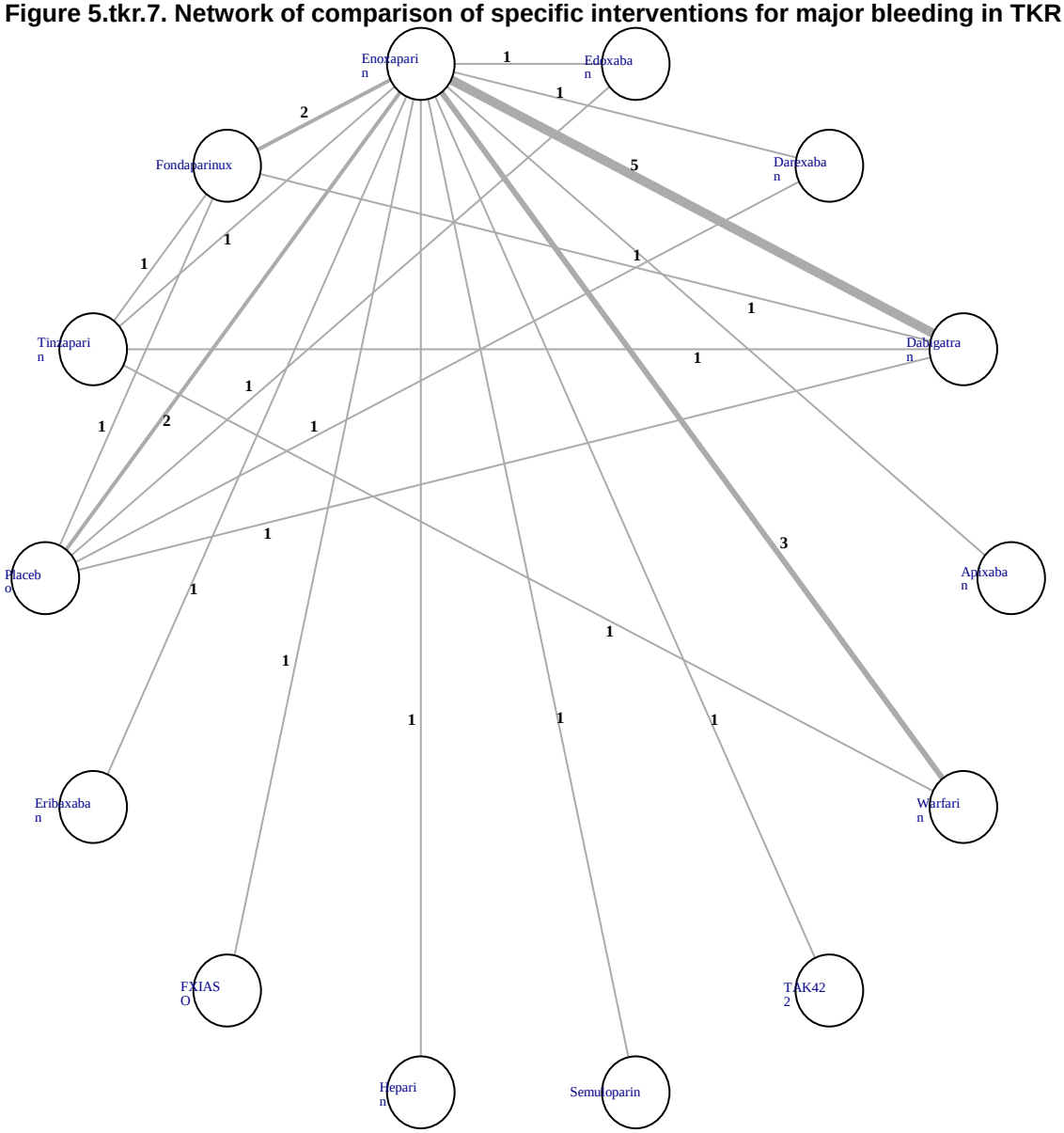


Distribution of probability (y-axis) of treatment rankings (x-axis) by intervention class based on network meta-analysis. Lower ranks indicate lower odds of outcome (greater benefit) with the given intervention compared with others.
Abbreviations: DTI = direct thrombin inhibitor, DVT = deep vein thrombosis, FXaI = factor Xa inhibitor, FXIi = factor XI inhibitor, LMWH = low molecular weight heparin, TKR = total knee replacement, UFH = unfractionated heparin, VKA = vitamin K antagonist.

Comparison of Specific Interventions

In the analysis by drug (or mechanical device), there were 23 RCTs that evaluated at least two interventions and reported major bleeding after TKR. However, one RCT of aspirin versus the combination of aspirin plus VFP did not connect to the network of evidence and was not included.[134] Hence, there were 22 RCTs in the network meta-analysis.[46, 49, 60, 75, 84-87, 90-95, 98-101, 108, 114, 118, 152] The RCTs compared pairs of interventions (20 RCTs), triplets of interventions (1 RCT), or quadruplets of interventions (1 RCT). Across this study set, 14 interventions were evaluated (apixaban, dabigatran, darexaban, edoxaban, enoxaparin, eribaxaban, fondaparinux, FXIASO, heparin, semuloparin, TAK422, tinzaparin, warfarin, placebo). Of the 91 possible pairwise comparisons, 21 are covered by direct study comparisons. **Figure 5.tkr.7** illustrates the topology of the network. Enoxaparin was the most common comparator, being directly compared with each of the 13 other interventions; most frequently with dabigatran (5 RCTs).

Figure 5.tkr.7. Network of comparison of specific interventions for major bleeding in TKR



Topology map for network meta-analysis of different interventions of thromboprophylaxis to avoid major bleeding outcome after total knee replacement. Nodes represent different interventions included in the analysis. Lines between nodes indicate the pairs of intervention classes that were compared directly within trials. The thickness of the lines is proportional to the number of trials directly comparing pairs of interventions, as indicated by the associated number.
Abbreviations: FXIASO = factor XI antisense oligonuclide, TKR = total knee replacement.

Appendix Table F7.8 shows the network meta-analysis pairwise results for all combinations of interventions. Results for comparisons with darexaban, edoxaban, fondaparinux, and FXIASO were not estimable (due to the following: there was one RCT of darexaban versus enoxaparin versus placebo which had rare events [1/88 versus 0/90 versus 0/96]; there was one RCT of edoxaban versus placebo with zero events and another RCT of edoxaban versus enoxaparin with rare events [4/354 versus 1/349]; two RCTs of fondaparinux had zero events and a third RCT versus enoxaparin had rare events [11/517 versus 1/517]; there was one RCT of FXIASO versus enoxaparin that had zero events).

Among interventions with sufficient data to allow reliable estimates (apixaban, dabigatran, enoxaparin, eribaxaban, heparin (unfractionated), semuloparin, TAK422, tinzaparin, and warfarin), no comparisons between interventions were found to have statistically significant differences in rates of major bleeding.

Summary

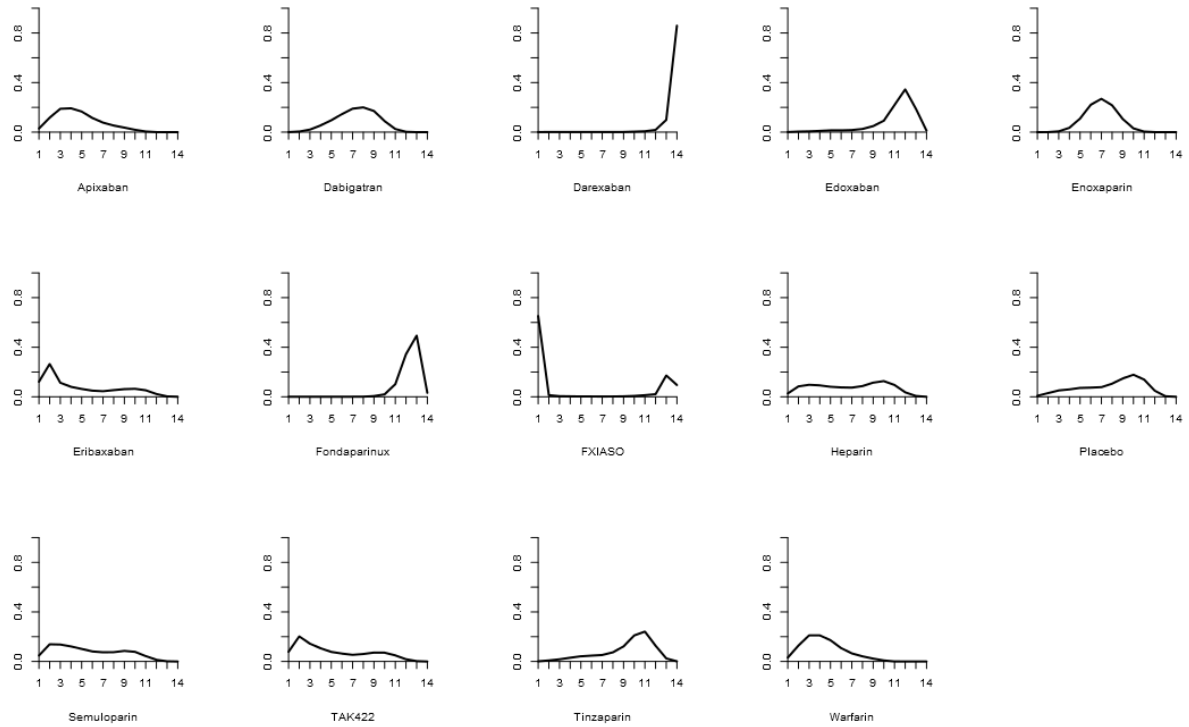
Across all comparisons, there were no statistically significant differences. Overall, FXIASO had the highest probability of being among the top three interventions (67%) to avoid major bleeding with thromboprophylaxis after TKR, followed by eribaxaban (61%). Notably, though the mechanical devices RCTs did not provide major bleeding data. The interventions likely to be among the bottom three interventions were darexaban (98%), fondaparinux (87%) and edoxaban (55%) (**Table 5.tkr.4**). The distribution of intervention ranks is provided in **Figure 5.tkr.8**. However, except for enoxaparin no intervention was directly compared to more than two other interventions by at least two RCTs each.

Table 5.tkr.4. Intervention ranking: Total knee replacement, intervention comparisons to avoid major bleeding

	Top 3 ranks	Bottom 3 ranks
Apixaban	33%	0%
Dabigatran	3%	0%
Darexaban	0%	98%
Edoxaban	1%	55%
Enoxaparin	1%	0%
Eribaxaban	50%	3%
Fondaparinux	0%	87%
FXIASO	67%	29%
Heparin	21%	4%
Semuloparin	32%	2%
TAK422	42%	2%
Tinzaparin	3%	15%
Warfarin	37%	0%
Placebo	9%	5%

Percent likelihood that each intervention falls within the top 3 or bottom 3 interventions in efficacy.
Abbreviations: FXIASO = factor XI antisense oligonuclide, TKR = total knee replacement.

Figure 5.tkr.8. Network meta-analysis ranks of interventions to avoid major bleeding in TKR



Distribution of probability (y-axis) of treatment rankings (x-axis) by intervention based on network meta-analysis. Lower ranks indicate lower odds of outcome (greater benefit) with the given intervention compared with others.
Abbreviations: IPC = intermittent pneumatic compression, THR = total hip replacement.

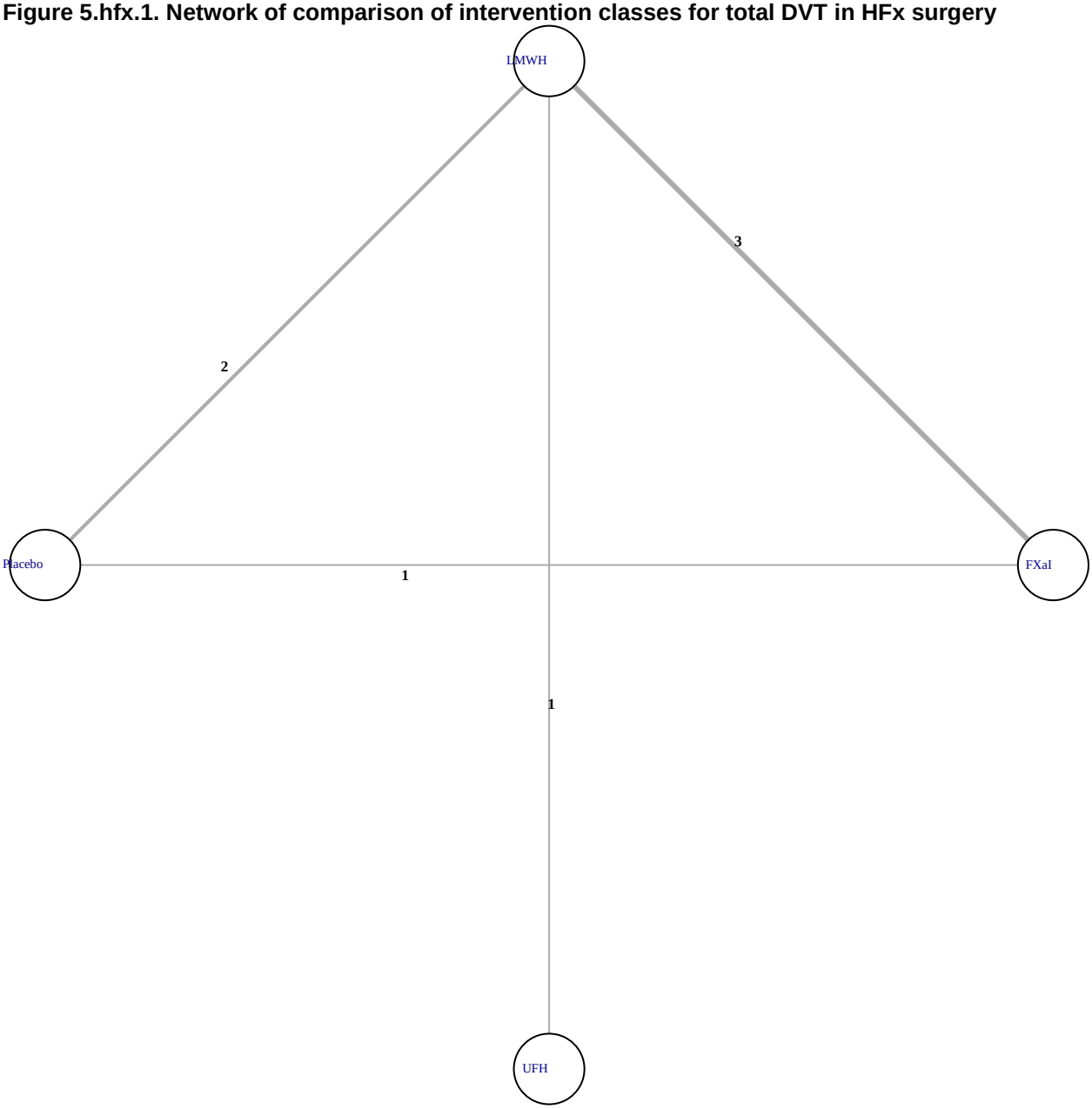
Hip Fracture Surgery

Deep Vein Thrombosis

Comparison of Classes

There were six RCTs that evaluated interventions in at least two classes and reported total DVT after HFx surgery. However, one RCT of antiplatelet drugs versus mechanical did not connect to the network of evidence.[102] Hence there were five RCTs included in the network meta-analysis.[104-107, 155] These RCTs compared pairs of intervention classes (four RCTs) or triplets of intervention classes (one RCT). Across this study set, four classes were evaluated (FXaI, LMWH, UFH, placebo). Of the six possible pairwise comparisons, four are covered by direct study comparisons. **Figure 5.hfx.1** illustrates the topology of the network. LMWH was directly compared with each of the three other intervention classes; FXaI was also directly compared with placebo.

Figure 5.hfx.1. Network of comparison of intervention classes for total DVT in HFx surgery



Topology map for network meta-analysis of different classes of thromboprophylaxis interventions for total deep vein thrombosis outcome after hip fracture surgery. Nodes represent different classes of interventions included in the analysis. Lines between nodes indicate the pairs of intervention classes that were compared directly within trials. The thickness of the lines is proportional to the number of trials directly comparing pairs of interventions, as indicated by the associated number.
Abbreviations: DVT = deep vein thrombosis, FXaI = factor Xa inhibitor, HFx = hip fracture, LMWH = low molecular weight heparin, UFH = unfractionated heparin.

Appendix Table F7.9 shows the network meta-analysis pairwise results for for all combinations of interventions classes. The statistically significant differences between classes are highlighted here.

- **FXaI** had a lower odds of DVT compared with
    - *LMWH* (OR=0.379; 95% CrI 0.269 to 0.525).

- **UFH** had a lower odds of DVT compared with
    - *LMWH* (OR=0.308; 95% CrI 0.091 to 0.949)

Summary

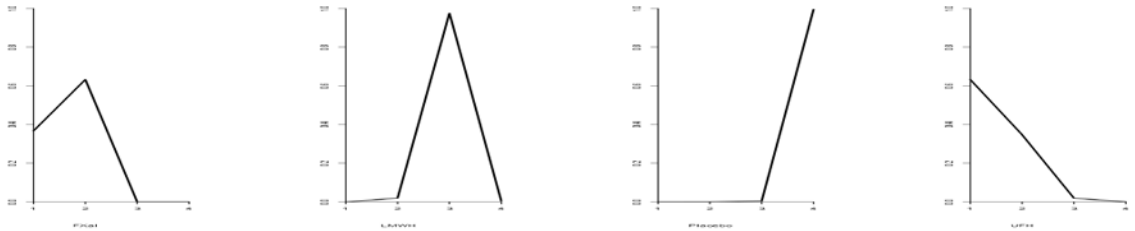
Overall, FXaI and UFH were likely to be among the top two interventions whereas placebo and LMWH were likely to be among the bottom two interventions (**Table 5.hfx.1**). The distribution of intervention ranks is provided in **Figure 5.hfx.2**. However, data were sparse and only LMWH was directly compared to more than two other interventions by at least two RCTs each (for two comparisons).

Table 5.hfx.1. Class ranking: Hip fracture surgery, intervention class comparisons to prevent DVT

	Top 2 ranks	Bottom 2 ranks
FXaI	100%	0%
LMWH	2%	98%
UFH	98%	2%
Placebo	0%	100%

Percent likelihood that each class falls within the top 2 or bottom 2 classes in efficacy.
Abbreviations: DVT = deep vein thrombosis, FXaI = factor Xa inhibitor, HFx = hip fracture, LMWH = low molecular weight heparin, UFH = unfractionated heparin.

Figure 5. hfx.2. Network meta-analysis ranks of intervention classes to prevent total DVT in HFx surgery

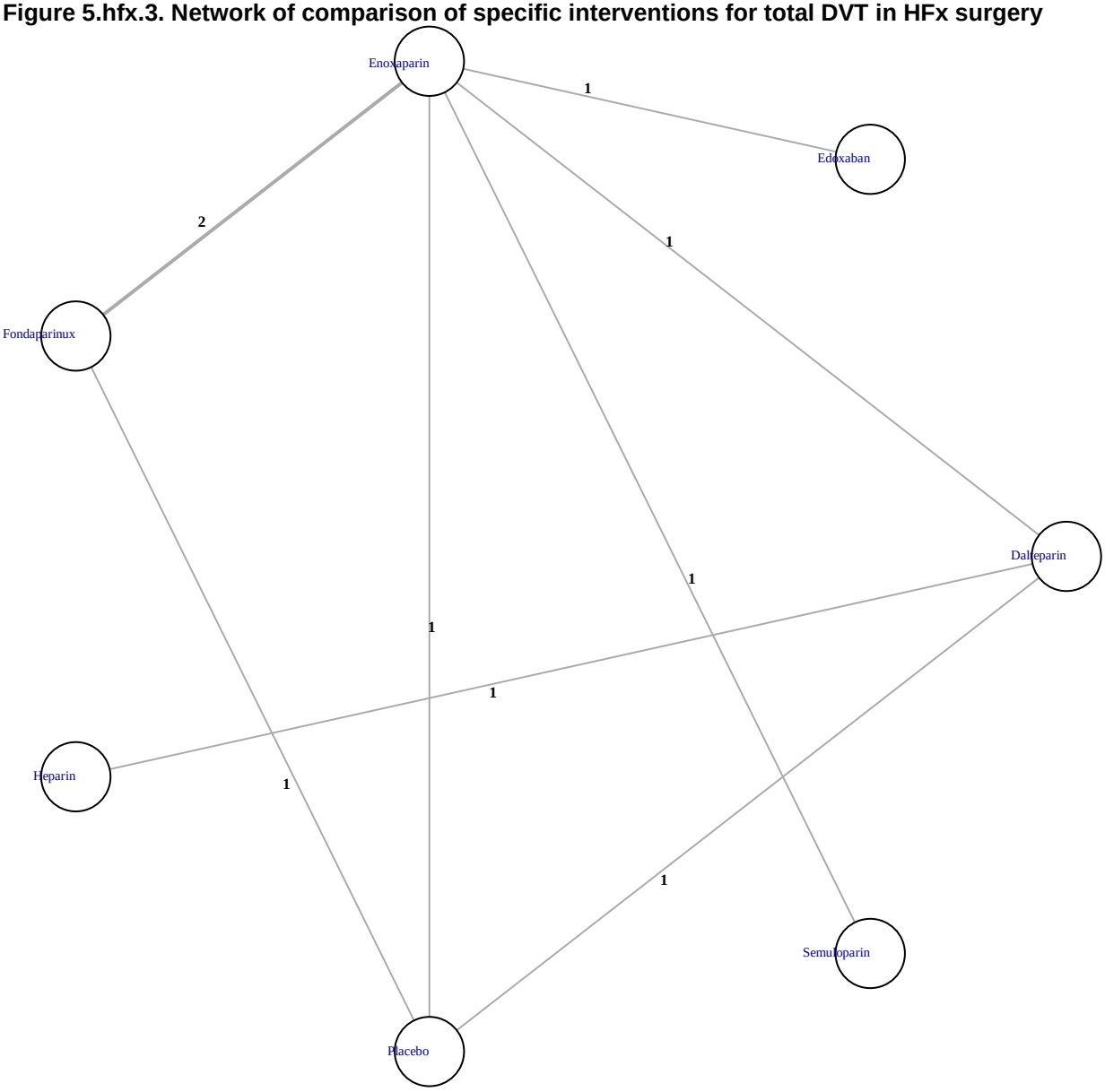


Distribution of probability (y-axis) of treatment rankings (x-axis) by intervention class based on network meta-analysis. Lower ranks indicate lower odds of outcome (greater benefit) with the given intervention compared with others.
Abbreviations: DVT = deep vein thrombosis, FXaI = factor Xa inhibitor, HFx = hip fracture, LMWH = low molecular weight heparin, UFH = unfractionated heparin.

Comparison of Specific Interventions

In the analysis by drug (or mechanical device), there were eight RCTs that evaluated at least two interventions and reported total DVT after HFx surgery. As with the analysis by class, there was one RCT of aspirin versus VFP which did not connect to the network of evidence.[102] Hence there were seven RCTs included in the network meta-analysis.[104-108, 112, 155] These RCTs compared pairs of interventions (six RCTs) or triplets of interventions (one RCT). Across this study set, seven interventions were evaluated (dalteparin, edoxaban, enoxaparin, fondaparinux, heparin, semuloparin, placebo). Of the 21 possible pairwise comparisons, 8 are covered by direct study comparisons. **Figure 5.hfx.3** illustrates the topology of the network. Enoxaparin was the most common comparator, being directly compared with five other interventions. Heparin was directly compared with dalteparin only.

Figure 5.hfx.3. Network of comparison of specific interventions for total DVT in HFx surgery



Topology map for network meta-analysis of different interventions of thromboprophylaxis for total deep vein thrombosis outcome after hip fracture surgery. Nodes represent different interventions included in the analysis. Lines between nodes indicate the pairs of intervention classes that were compared directly within trials. The thickness of the lines is proportional to the number of trials directly comparing pairs of interventions, as indicated by the associated number.
Abbreviations: DVT = deep vein thrombosis, HFx = hip fracture surgery.

Appendix Table F7.10 shows the network meta-analysis pairwise results for all combinations of interventions. The statistically significant differences between active interventions are highlighted here.

- **Heparin** had a lower odds of DVT compared with
  - *dalteparin* (OR=0.306; 95% CrI 0.092 to 0.937)
  - *edoxaban* (OR=0.058; 95% CrI 0.001 to 0.934)
  - *enoxaparin* (OR=0.136; 95% CrI 0.029 to 0.587)

    - *semuloparin* (OR=0.187; 95% CrI 0.038 to 0.835)
- **Fondaparinux** had a lower odds of DVT compared with
    - *enoxaparin* (OR=0.358; 95% CrI 0.253 ro 0.501)
    - *semuloparin* (OR=0.491; 95% CrI 0.298 to 0.811).

Summary

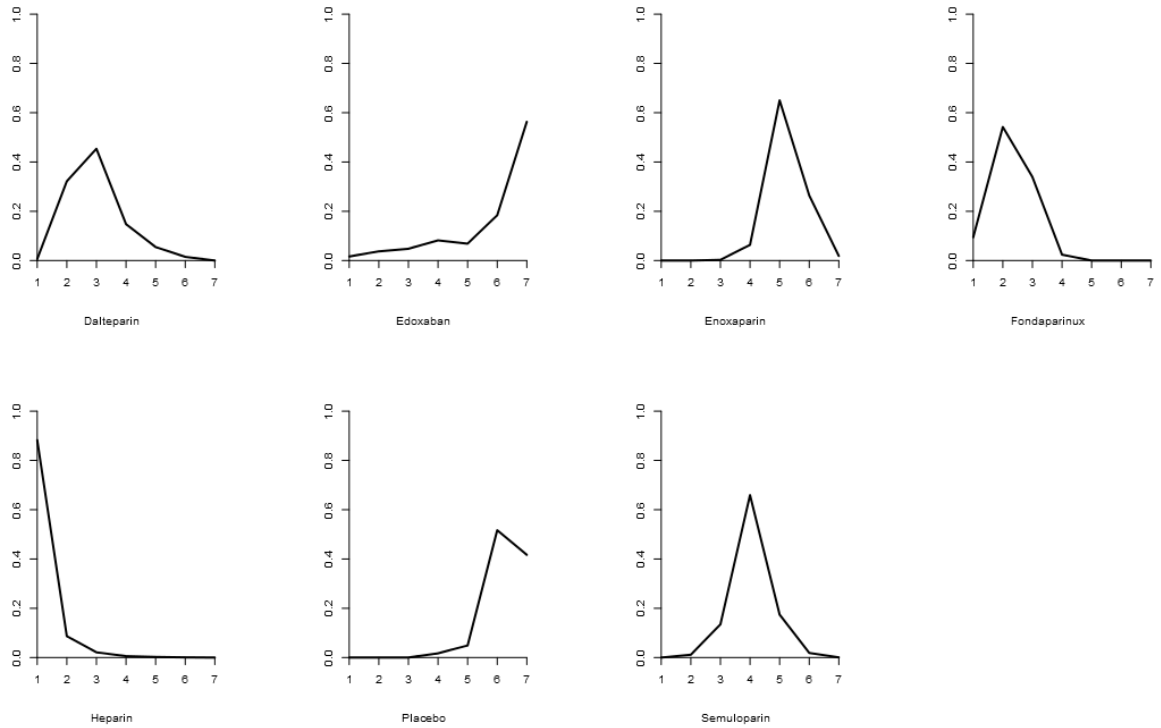
Overall, heparin (99%) and fondaparinux (98%) had the highest probabilities of being among the top three interventions to prevent DVT after HFx surgery, followed by dalteparin (78%). The other three interventions were likely to be among the bottom three interventions: placebo (98%), enoxaparin (93%), and edoxaban (82%) (**Table 5.hfx.2**). The distribution of intervention ranks is provided in **Figure 5.hfx.4**. However, no intervention was directly compared to two other interventions by at least two RCTs.

Table 5.hfx.2. Intervention ranking: Hip fracture surgery, intervention comparisons to prevent DVT

	Top 3 ranks	Bottom 3 ranks
Dalteparin	78%	7%
Edoxaban	10%	82%
Enoxaparin	0%	93%
Fondaparinux	98%	0%
Heparin	99%	0%
Semuloparin	15%	19%
Placebo	0%	98%

Percent likelihood that each intervention falls within the top 3 or bottom 3 interventions in efficacy.
Abbreviations: DVT = deep vein thrombosis.

Figure 5.hfx.4. Network meta-analysis ranks of interventions to prevent total DVT in HFx surgery



Distribution of probability (y-axis) of treatment rankings (x-axis) by intervention based on network meta-

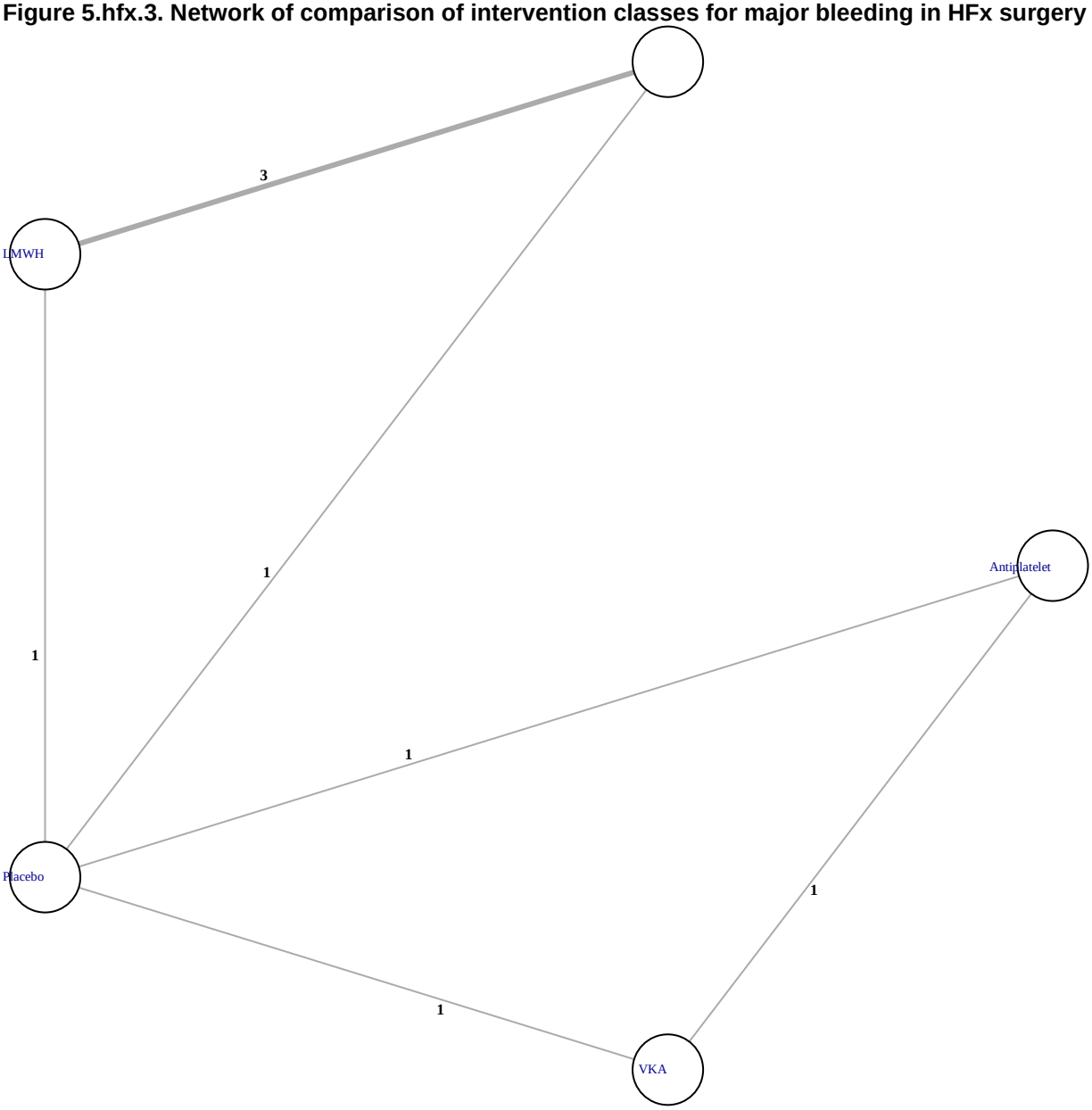
analysis. Lower ranks indicate lower odds of outcome (greater benefit) with the given intervention compared with others.
Abbreviations: DVT = deep vein thrombosis, HFx = hip fracture surgery.

Major Bleeding

Comparison of Classes

There were four RCTs that evaluated interventions in at least two classes and reported major bleeding after HFx surgery.[103-106] The RCTs compared pairs of intervention classes (two RCTs) or triplets of intervention classes (two RCTs). Across this study set, five classes were evaluated (antiplatelet drugs, FXaI, LMWH, VKA, placebo). Of the 10 possible pairwise comparisons, 6 are covered by direct study comparisons. **Figure 5.hfx.5** illustrates the topology of the network. Placebo was the most common comparator, being directly compared with each of the five other intervention classes.

Figure 5.hfx.3. Network of comparison of intervention classes for major bleeding in HFx surgery



Topology map for network meta-analysis of different classes of thromboprophylaxis interventions for major bleeding outcome after hip fracture surgery. Nodes represent different classes of interventions included in the analysis. Lines between nodes indicate the pairs of intervention classes that were compared directly within trials. The thickness of the lines is proportional to the number of trials directly comparing pairs of interventions, as indicated by the associated number.
Abbreviations: FXaI = factor Xa inhibitor, HFx = hip fracture, LMWH = low molecular weight heparin, VKA = vitamin K antagonist.

Appendix Table F7.11 shows the network meta-analysis pairwise results for all combinations of interventions. Results for comparisons versus antiplatelet drugs and VKA were not estimable (due to the following: there was one RCT of antiplatelet drugs versus VKA versus placebo which had a small sample size and rare events [1/66 vs. 5/65 vs. 5/63]). Among interventions with sufficient data to allow reliable estimates (FXaI and LMWH), the comparison between interventions was not statistically significant regarding rates of major bleeding.

Summary

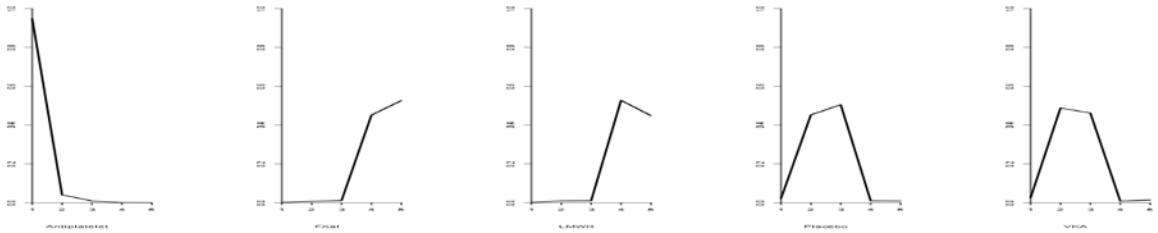
There were no statistically significant differences. Overall, antiplatelet drugs had the highest probability of being among the top two interventions (>99%) to avoid major bleeding with thromboprophylaxis after HFx surgery, followed by VKA (51%). The interventions likely to be among the bottom two interventions were FXaI (98%) and LMWH (98%) (**Table 5.hfx.3**). The distribution of intervention ranks is provided in **Figure 5.hfx.6**. However, except for the comparison of LMWH and FXaI, only single RCTs compared intervention classes.

Table 5.hfx.3. Class ranking: Hip fracture surgery, intervention comparisons to avoid major bleeding

	Top 2 ranks	Bottom 2 ranks
Antiplatelet	99%	0%
FXaI	1%	98%
LMWH	1%	98%
VKA	51%	2%
Placebo	47%	2%

Percent likelihood that each class falls within the top 2 or bottom 2 classes in efficacy.
Abbreviations: FXaI = factor Xa inhibitor, HFx = hip fracture, LMWH = low molecular weight heparin, VKA = vitamin K antagonist.

Figure 5.hfx.6. Network meta-analysis ranks of intervention classes to avoid major bleeding in HFx surgery

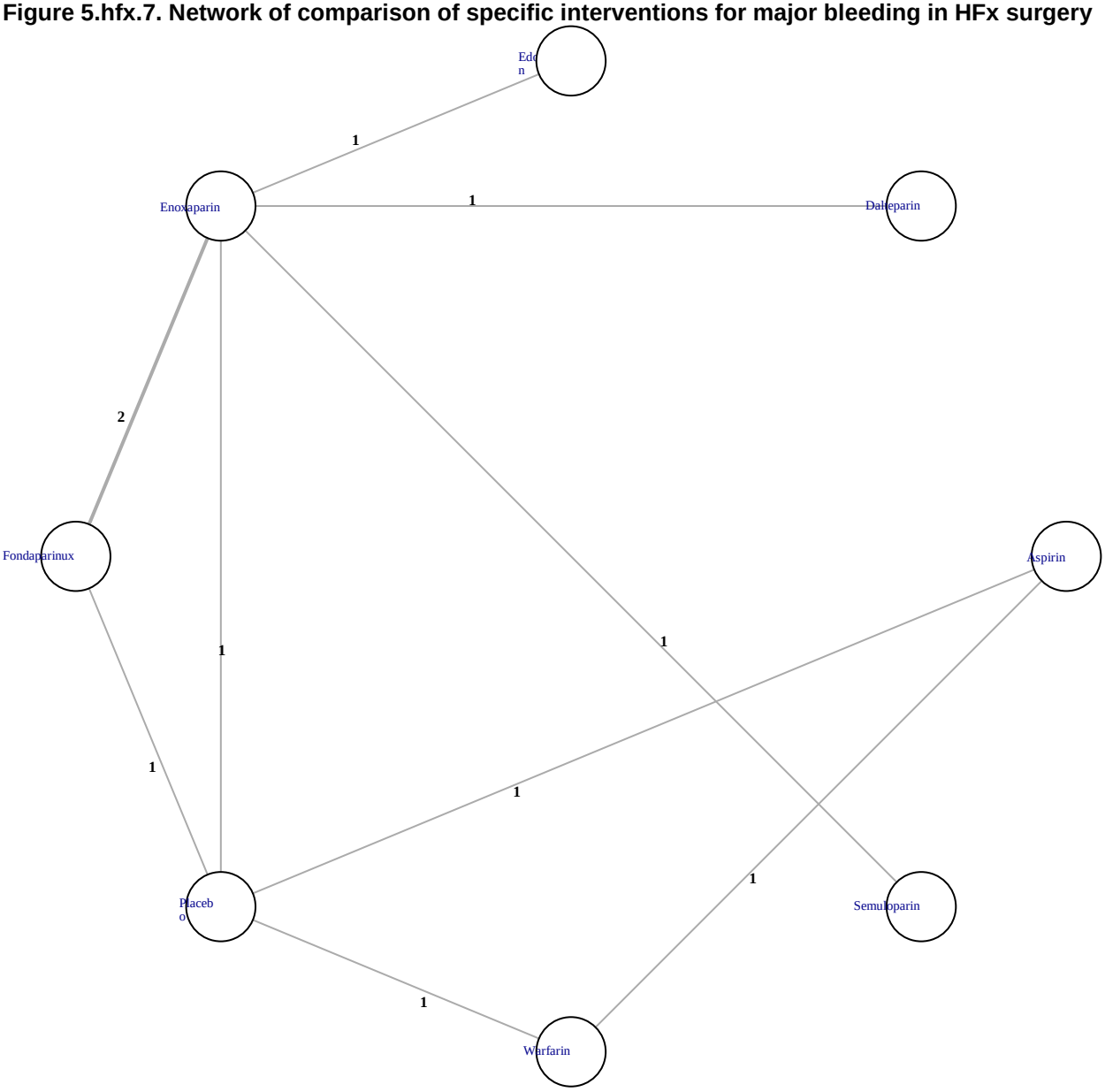


Distribution of probability (y-axis) of treatment rankings (x-axis) by intervention class based on network meta-analysis. Lower ranks indicate lower odds of outcome (greater benefit) with the given intervention compared with others.
Abbreviations: FXaI = factor Xa inhibitor, HFx = hip fracture, LMWH = low molecular weight heparin, VKA = vitamin K antagonist.

Comparison of Specific Interventions

In the analysis by drug (or mechanical device), there were six RCTs that evaluated at least two interventions and reported major bleeding after HFx surgery.[103-106, 108, 112] The RCTs compared pairs of interventions (four RCTs) or triplets of interventions (two RCTs). Across this study set, eight interventions were evaluated (aspirin, dalteparin, edoxaban, enoxaparin, fondaparinux, semuloparin, warfarin, placebo). Of the 28 possible pairwise comparisons, 9 are covered by direct study comparisons. **Figure 5.hfx.7** illustrates the topology of the network. Enoxaparin was the most common comparator, being directly compared with five other interventions. Aspirin and warfarin were directly compared with each other and placebo only.

Figure 5.hfx.7. Network of comparison of specific interventions for major bleeding in HFx surgery



Topology map for network meta-analysis of different interventions of thromboprophylaxis for major bleeding outcome after hip fracture surgery. Nodes represent different interventions included in the analysis. Lines between nodes indicate the pairs of intervention classes that were compared directly within trials. The thickness of the lines is proportional to the number of trials directly comparing pairs of interventions, as indicated by the associated number.
Abbreviations: HFx = hip fracture.

Appendix Table F7.12 shows the network meta-analysis pairwise results for all combinations of interventions. Results for comparisons with aspirin and warfarin were not estimable (due to the following: there was one RCT of aspirin versus warfarin versus placebo which had a small sample size and rare events [1/66 vs. 5/65 vs. 5/63]). Among interventions with sufficient data to allow reliable estimates (dalteparin, edoxaban, fondaprinux, and semuloparin), all comparisons between interventions were not statistically significant regarding rates of major bleeding.

Summary

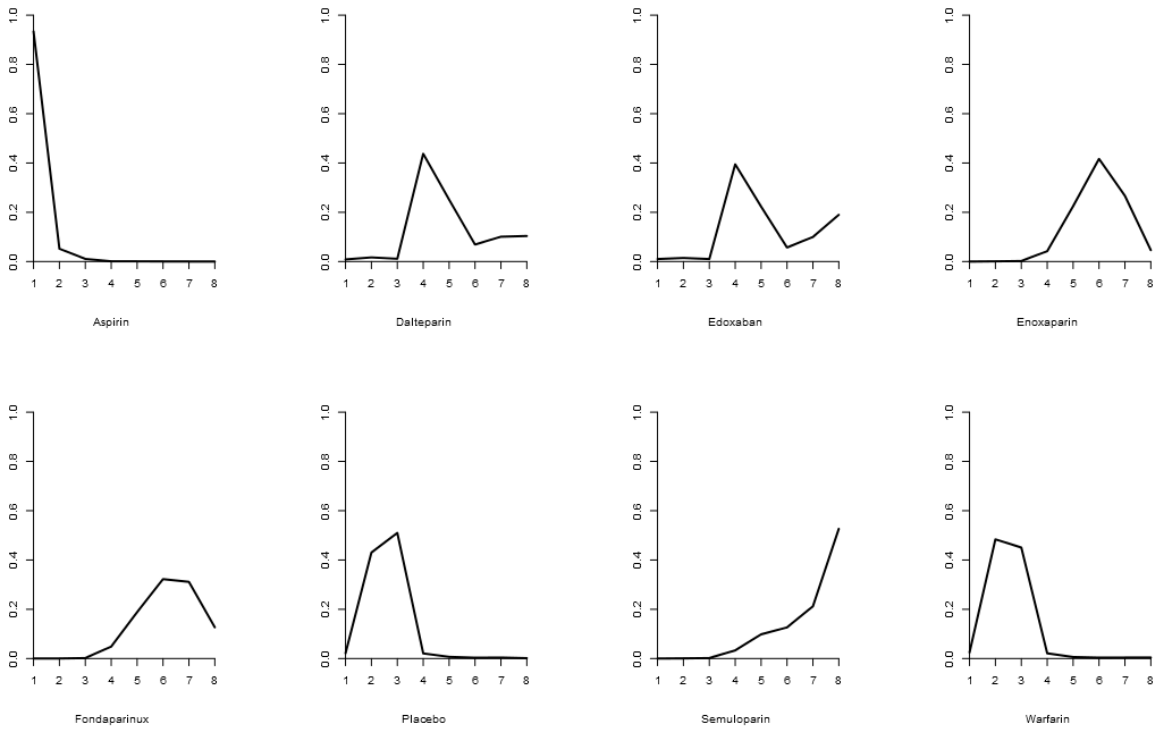
There were no statistically significant differences. Overall, aspirin had the highest probability of being among the top three interventions (>99%) to avoid major bleeding with thromboprophylaxis after HFx surgery, followed by placebo (96%) and warfarin (96%). The interventions likely to be among the bottom three interventions were semuloparin (87%), fondaparinux (76%), and enoxaparin (73%) (**Table 5.hfx.4**). The distribution of intervention ranks is provided in **Figure 5.hfx.8**. However, only enoxaparin and fondaparinux were directly compared by two RCTs.

Table 5.hfx.4. Intervention ranking: Hip fracture surgery, intervention comparisons to avoid major bleeding

	Top 3 ranks	Bottom 3 ranks
Aspirin	100%	0%
Dalteparin	4%	27%
Edoxaban	4%	35%
Enoxaparin	0%	73%
Fondaparinux	0%	76%
Semuloparin	0%	87%
Warfarin	96%	1%
Placebo	96%	1%

Percent likelihood that each intervention falls within the top 3 or bottom 3 interventions in efficacy.
Abbreviations: HFx = hip fracture.

Figure 5.hfx.8. Network meta-analysis ranks of interventions to avoid major bleeding in HFx surgery



Distribution of probability (y-axis) of treatment rankings (x-axis) by intervention based on network meta-analysis. Lower ranks indicate lower odds of outcome (greater benefit) with the given intervention compared with others.

Abbreviations: HFx = hip fracture.

Total DVT and Major Bleeding Rate Estimates, by Surgery and Class

Based on RCTs included in the network meta-analysis, we estimated rates of total DVT and major bleeding for each intervention class (with estimable data), by surgery type. These estimates are based on the summary estimates (and 95% CI) of total DVT and major bleeding for patients who received LMWH (the class with the most RCT data) and the OR for each available class compared to LMWH. The estimates are presented in **Tables XX1 and XX2.**

Table XX1. Estimated proportion of patients with total DVT after surgery, by intervention class

Surgery	Class	Event Proportion (95% CI)
THR	LMWH + Mechanical	0.050 (0.001, 0.303)
	FXaI	0.066 (0.001, 0.369)
	FEI	0.073 (0.001, 0.395)
	DTI	0.090 (0.001, 0.452)
	Mechanical	0.115 (0.001, 0.520)
	Antiplatelet	0.119 (0.002, 0.529)
	LMWH	0.127 (0.002, 0.548)
	UFH	0.174 (0.002, 0.637)
	VKA	0.183 (0.002, 0.651)
TKR	Antiplatelet + Mechanical	0.086 (0.001, 0.283)
	FXaI	0.119 (0.002, 0.361)
	DTI	0.136 (0.002, 0.397)
	LMWH + Mechanical	0.141 (0.002, 0.406)
	FXiI	0.180 (0.002, 0.478)
	LMWH	0.219 (0.003, 0.539)
	Mechanical	0.225 (0.003, 0.548)
	UFH	0.296 (0.005, 0.637)
	VKA	0.332 (0.005, 0.675)
	Antiplatelet	0.348 (0.006, 0.690)
HFx	UFH	0.095 (0.002, 0.292)
	FXaI	0.114 (0.002, 0.336)

Within surgery type, intervention classes ordered from lowest to highest estimated DVT rates.
Abbreviations: CI = confidence interval, DTI = direct thrombin inhibitor, DVT = deep vein thrombosis, FEI = factor VIII inhibitor, FXaI = factor Xa inhibitor, FXiI = factor Xi inhibitor, HFx = hip fracture surgery, LMWH = low molecular weight heparin, THR = total hip replacement, TKR = total knee replacement, UFH = unfractionated heparin, VKA = vitamin K antagonist.

Table XX2. Estimated proportion of patients with major bleeding after surgery, by intervention class

Surgery	Class	Event Proportion (95% CI)
THR	Mechanical	0 (not estimable)
	VKA	0.011 (0.001, 0.035)
	LMWH	0.018 (0.001, 0.058)
	DTI	0.023 (0.001, 0.072)
	FXaI	0.025 (0.002, 0.078)
	UFH	0.040 (0.003, 0.119)
	Antiplatelet	Not estimable
	FEI	Not estimable
TKR	VKA	0.007 (0.001, 0.027)
	LMWH	0.015 (0.002, 0.052)
	UFH	0.015 (0.002, 0.053)
	DTI	0.016 (0.002, 0.055)
	FXaI	0.020 (0.003, 0.070)
	FXiI	Not estimable
HFx	Antiplatelet	0 (not estimable)
	VKA	0 (not estimable)
	LMWH	0.023 (0.004, 0.035)
	FXaI	0.024 (0.004, 0.036)

Within surgery type, intervention classes ordered from lowest to highest estimated major bleeding rates. Abbreviations: CI = confidence interval, DTI = direct thrombin inhibitor, FEI = factor VIII inhibitor, FXaI = factor Xa inhibitor, FXiI = factor Xi inhibitor, HFx = hip fracture surgery, LMWH = low molecular weight heparin, THR = total hip replacement, TKR = total knee replacement, UFH = unfractionated heparin, VKA = vitamin K antagonist.

Key Question 6

In patients undergoing major orthopedic surgery, what is the comparative efficacy of starting pharmacologic thromboprophylaxis at different times (i.e., preoperative, intraoperative, postoperative) on venous thromboembolism outcomes, major bleeding, other adverse events, and treatment adherence?

Total Hip Replacement

LMWH Preoperative Versus Postoperative Start

Two RCTs (N=1063) compared LMWH started preoperatively versus postoperatively (**Table X14**).[76, 156] One study found no significant difference in total DVT and proximal DVT, and reported no total PE, and no fatal PE. The other study found no significant difference in symptomatic PE. The two studies reported symptomatic DVT; one found no significant difference, and the other reported no events.

One RCT found no significant difference in major bleeding and 30-day mortality, and reported no fatal bleeding. The other study found no significant difference in bleeding leading to reoperation. Two studies found no significant difference in bleeding at surgical site or joint.

The studies did not report on adherence.

Total Knee Replacement

No eligible studies evaluated patients with TKR.

Hip Fracture Surgery

No eligible studies evaluated patients with HFx surgery.

Table X14. Results summary: Total hip replacement, treatment initiation time comparisons

Comparison	Outcome	Studies, N	Patients, N	OR, 1	OR, 2	OR, 3	No Events*
LMWH_Preop vs. LMWH_Postop	PE, Total	1	983	No estimate			1 RCT
	PE, Fatal	1	983	No estimate			1 RCT
	PE, Symptomatic	1	80	0.33 (0.01, 8.22)			
	DVT, Total	1	673	0.79 (0.50, 1.27)			
	DVT, Symptomatic	2	753	0.49 (0.17, 1.45)			1 RCT
	DVT, Proximal	1	712	1.01 (0.20, 5.05)			
	Bleeding, Major	1	983	1.17 (0.69, 1.97)			
	Bleeding, Fatal	1	983	No estimate			1 RCT
	Bleeding, Leading to reoperation	1	80	3.08 (0.12, 77.8)			
	Bleeding, Surgical site/joint	2	1063	0.73 (0.15, 3.49)	1.17 (0.69, 1.99)		
	Mortality, 30 day or in-hospital	1	983	4.93 (0.24, 103)			

All outcomes for all pairwise comparisons with data from at least one study. If 3 or fewer randomized controlled trials (RCT) with analyzable data (i.e., at least 1 event per study) then each study's odds ratio (OR) is listed in ascending order from left to right. If there were ≥4 analyzable studies, then meta-analysis was conducted and summary OR is reported. These are indicated by italics and by MA (meta-analysis) in the study number column. Statistically significant OR estimates are in bold text. The corresponding studies for each analysis can be found in Appendix F.
Other abbreviations: DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venothromboembolism, LMWH = low molecular weight heparin, Preop = preoperative, Postop = postoperative, vs. = versus.
* Number of RCTs with no events in both arms.

Overall Summary and Strength of Evidence

Total Hip Replacement

Across Key Questions, 81 eligible studies evaluated thromboprophylaxis interventions in patients who underwent THR. The largest number compared different classes of interventions (relevant to Key Questions 1 and 5). The most commonly evaluated intervention class was LMWH, mostly in comparison with DTI, FXaI, UFH, and VKA. Other interventions were relatively infrequently evaluated in comparative effectiveness trials (i.e., comparisons of active, nonplacebo interventions). The most commonly evaluated outcomes were total DVT and major bleeding. Strength of evidence is summarized in **Table EP1.**

Key Question 1: Comparison of Intervention Classes

Note that for all three surgeries, network meta-analyses comparing classes in regard to total DVT and major bleeds are presented under Key Question 5. The results of comparisons with what was deemed to have sufficient evidence are summarized here; other comparisons are noted, but were deemed to have insufficient evidence.

Key Points

- 44 RCTs and 5 NRCSs compared classes of interventions in patients undergoing THR.
- Pairwise comparisons between classes had sufficient data for only five pairs of classes.
  - LMWH vs. DTI: Overall favors DTI, with lower risk of VTE (total DVT and proximal DVT; moderate to high SOE) and similar risk of major bleeding (high SoE).
  - LMWH vs. FXaI: Overall, favors LMWH, with an unclear difference in effect on risk of VTE (low to moderate SoE of inconsistent results), but lower risk of bleeding with LMWH (high SoE). There were statistically significant differences for total VTE (favoring FXaI), symptomatic VTE (favoring LMWH), and proximal DVT (favoring LMWH), but no significant difference in symptomatic DVT; the inconsistencies in these finding suggest important reporting bias.
  - LMWH vs. UFH: Overall, favors LMWH, with lower risk of VTE (total PE, proximal DVT), but similar risk of total DVT; moderate to high SoE) and lower risk of major bleeding (moderate SoE).
  - LMWH vs. VKA: Overall, an apparent tradeoff in risks with lower risk of total DVT with LMWH (high SoE), similar risks of proximal DVT (low SoE), and lower risk of major bleeding with VKA (high SoE).
  - Mechanical vs. UFH: Overall, unclear. It is unclear which intervention class has higher risk of total DVT (low SoE), UFH results in lower risk of proximal DVT (high SoE), but insufficient evidence regarding adverse events.
  - For all other class comparisons and outcomes there was insufficient evidence.
  - Although studies reasonably should have had data for all VTE-related outcomes and for major bleeding and other serious adverse events, most outcomes were not reported by many studies, resulting in a high risk of reporting bias across the evidence base.
- A within-study subgroup analysis was inconclusive regarding differential risks of bleeding with LMWH and DTI by CKD stage.
- Industry-funded studies had similar finding as other studies. Asian studies had similar findings as non-Asian studies.

Summary Results

Pairwise comparisons between classes had sufficient data for five pairs of classes. For the comparison of **LMWH vs. DTI**, among four RCTs, three favored DTI to prevent total DVT and three favored DTI to prevent proximal DVT. Meta-analysis of the four tirals did not find a significant difference between drug classes regarding major bleeding.

For the comparison of **LMWH versus FXaI**, among 11 RCTs there is high risk of reporting bias for several of the outcomes. Most meta-analyses of VTE outcomes significantly favored FXaI (total VTE [7 RCTs], total DVT [9 RCTs], proximal DVT [10 RCTs]). However, the meta-analysis of symptomatic VTE significantly favored LMWH over FXaI, but the RCTs reporting symptomatic VTE largely did not report other VTE outcomes. The meta-analysis of symptomatic DVT (8 RCTs) was imprecise and found no significant difference between drug classes. Major bleeding was significantly less likely with LMWH (across 9 RCTs), but there was no significant difference in serious adverse events (5 RCTs).

Among 3 RCTs of **LMWH versus mechanical devices**, there was insufficient evidence and it was unclear how the interventions compare.

From 10 RCTs, meta-analyses of **LMWH versus UFH** significantly favored LMWH to prevent total PE (8 RCTs) and proximal DVT (6 RCTs) and to avoid major bleeding (6 RCTs), but showed no statistically significant difference in total DVT (10 RCTs) and symptomatic DVT (4 RCTs that yielded an imprecise estimate).

Meta-analysis of tehe 4 RCTs of LMWH versus VKA found significantly lower rates of major bleeding with VKA. Three of the RCTs favored LMWH to prevent total DVTs. Results for other outcomes were unclear.

Three RCTs evaluated **mechanical devices versus UFH**, favoring VKA to prevent proximal DVTs, but yielding unclear results regarding total DVT.

Other intervention classes compared by fewer studies (with insufficient evidence) included antiplatelet drugs versus VKA, DTI versus FXaI, DTI versus UFH, and FEI versus FXaI.

Subgroup Analysis

One RCT reported results for serious bleeding by level of chronic kidney disease (CKD) in a comparison of LMWH and DTI. Event rates were low for all participants (2% in both the desirudin and the enoxaparin arms). They reported that for CKD stage 3B (n=569), more patients experienced a major bleed in the desirudin arm than in the enoxaparin arm, although the difference was not statistically significant (1.8% vs. 0.3%; P = 0.112). For CKD 3A (n=758), the rates were the same (0.3% in both arms). For CKD 1-2 (n=700), DVT rates were also lower in the enoxaparin arm (0.6% vs. 0%).

Studies were generally homogeneous in terms of patient eligibility criteria, such that most studies included all-comers without eligibility restrictions based on demographics, or other major patient or surgery subtypes. While some studies were restricted based on past bleeding history or chronic antiplatelet or VKA use, no RCTs were restricted to the converse populations (only patients with bleeding history or on antithromobotic medication). Thus, across-study comparisons of subgroup factors are limited.

Among THR RCTs, differences between studies based on industry funding was analyzable for only the comparison of LMWH versus UFH. For total DVT, by random effects model metaregresion no significant difference (P=0.51) was found between the eight industry-funded studies (summary OR 0.91, 95% CI 0.59 to 1.41) and the two studies without reported industry support (summary OR 0.71, 95% CI 0.38 to 1.32). Similarly, for major bleeding, no significant

difference (P=0.95) was found between the four industry-funded studies (summary OR 0.62, 95% CI 0.13 to 2.93) and the two studies without industry support (summary OR 0.56, 95% CI 0.26 to 1.20).

For the comparison of Asian versus non-Asian RCTs, only the comparison of LMWH versus FXaI was analyzable. For total DVT, no significant difference (P=0.56) was found between the five Asian studies (summary OR 1.63, 95% CI 0.81 to 3.31) and the four non-Asian studies (summary OR 2.08, 95% CI 1.40 to 3.09) by random effects model metaregresion. The non-Asian studies included more patients, largely explaining the difference in statistical significance between the two sets of studies. Overall, the same percentage of Asian and non-Asian study participants had a DVT among these RCTs (4.7%). Similarly, for major bleeding, no significant difference (P=0.16) was found between the four Asian RCTs with major bleeding events (summary OR 1.95, 95% CI 0.46 to 8.22) and the five non-Asian studies (OR 0.68, 95% CI 0.49 to 0.94). Again, the non-Asian studies included more patients, largely explaining the difference in statistical significance between the two sets of studies. The Asian RCTs had relatively few events, with an overall major bleeding rate of 0.7 percent compared to 1.5 percent among all non-Asian RCTs (P=0.041); however, if the European study with an atypically high reported major bleeding rate (3.5%) is excluded, the non-Asian RCTs have a major bleeding rate of 0.9 percent, similar to the reported Asian rate (P=0.59).

Key Question 2: Comparison of Within-Class Interventions

Note that for all three surgeries, network meta-analyses comparing individual interventions in regard to total DVT and major bleeds are presented under Key Question 5.

Relatively few RCTs of venoprophylaxis compared specific interventions within any given class (3 for THR). No comparison was evaluated by more than two studies.

In patients undergoing THR, one or two RCTs each evaluated enoxaparin versus semuloparin (LMWHs), enoxaparin versus tinzaparin (LMWHs), and graduated compression stockings versus intermittent pressure devices (mechanical devices). Evidence was insufficient to evaluate within-class intervention comparisons.

Key Question 3: Comparison of Dosages and Treatment Durations

Key Points

- 22 RCTs and 2 NRCSs compared different intervention doses or durations in patients undergoing THR
- FXaI low vs. high dose: There is low SoE that high dose FXaI yields a lower risk of total VTE, but insufficient evidence for other outcomes
- LMWH low vs. high dose: There is moderate SoE that low dose LMWH yields a lower risk of total DVT, but low SoE of an unclear difference to prevent proximal DVT and insufficient evidence for other outcomes.
- LMWH short vs. long duration: There is moderate to high SoE that long duration LMWH results in lower risk of VTE (total PE, total DVT, and proximal DVT), but insufficient evidence for adverse events.

More than 300 specific comparisons of different drug doses or device regimens have been reported; the large majority of specific comparisons were made by a single study only. Comparisons with sufficient evidence are summarized here. These all pertain to class-level

analyses; specific intervention comparisons were not evaluated with sufficient frequency to allow a conclusion of sufficient evidence.

For three pairwise comparisons of dose or treatment duration, there was sufficient data. Five RCTs comparing **FXaI low versus high doses** favored high dose FXaI to prevent total VTE, but the summary OR was not statistically significant.

Five RCTs of **LMWH low versus high doses** significantly favored low dose LMWH to prevent DVT, but it was unclear whethere low or high dose LMWH better prevented proximal DVT (4 RCTs).

Among 6 RCTs of **LMWH short versus long duration treatment**, long duration LMWH resulted in fewer total PE (5 RCTs), but the summary OR was not statistically significant. Long duration LMWH resulted in statistically significantly lower risk of total DVT (6 RCTs) and proximal DVTs (5 RCTs).

Key Question 4: Comparison of Single Versus Combination Classes

Note that for all three surgeries, network meta-analyses comparing individual interventions (including combination interventions) in regard to total DVT and major bleeds are presented under Key Question 5. However, in pairwise comparisons, relatively few studies directly compared combination versus single interventions. Most specific comparisons were made by one study only.

For THR, RCTs provided insufficient evidence for comparisons of antiplatelet drug versus antiplatelet drug and mechanical device; LMWH alone versus combinations of LMWH and antiplatelet drug, DTI, FXaI, and mechanical device; mechanical device alone versus the mechanical device and antiplatelet drug, both antiplatelet drug and UFH, and VKA; and UFH alone versus combination UFH and LMWH. In addition, one RCT compared combination antiplatelet drug and UFH versus combination antiplatelet device, UFH, and mechanical device.

Key Question 5: Network Meta-Analyses

Key Points

- Conclusions from all NMAs are limited due to the sparseness of direct comparisons between most interventions within each network.
- For patients undergoing THR, NMA suggests that
  - By class
    - Among 50 RCTs, FXaI is most effective to prevent total DVT, followed by DTI, mechanical devices, LMWH, VKA, and UFH (moderate SoE).
    - Among 30 RCTs, LMWH resulted in fewer major bleeding events than FXaI, and placebo was least likely to cause major bleeding (low SoE).
  - By intervention,
    - Among 50 RCTs, dalteparin is most effective to prevent total DVTs, followed by enoxaparin, (unfractionated) heparin, and, finally, warfarin (moderate SoE).
    - Despite 31 RCTs, comparisons between specific pairs of interventions were too sparse to yield sufficient conclusions regarding risk of major bleeding.

DVT: Comparison of Classes

There were 50 RCTs that evaluated interventions in at least two classes and reported total DVT after THR. Across this study set, 10 classes were evaluated (antiplatelet drugs, DTI, FEI, FXaI, LMWH, LMWH+mechanical, mechanical, UFH, VKA, placebo). Of the 45 possible pairwise comparisons, 17 are covered by direct study comparisons. LMWH was the most common comparator, being directly compared with seven other intervention classes, most frequently with FXaI (9 RCTs), UFH (10 RCTs) and placebo (11 RCTs). Antiplatelet drugs were directly compared with placebo and VKA only; FEI was directly compared with FXaI only.

Overall, the combination of LMWH plus mechanical intervention had the highest probability of being among the top three intervention classes (88%) to prevent DVT in patients undergoing THR, followed by FXaI (85%). The interventions likely to be among the bottom three interventions were placebo (>99%), UFH (87%), and VKA (85%) However, omitting interventions that are directly linked to two or fewer other interventions with two or fewer RCTs each (antiplatelet drugs, FEI, and combined LMWH and mechanical devices), FXaI is most effective to prevent total DVT, followed by DTI, mechanical devices, LMWH, VKA, and UFH.

DVT: Comparison of Specific Interventions

In the analysis by drug (or mechanical device), there were 51 RCTs that evaluated at least two interventions and reported total DVT after THR. However, one RCT of TB402 versus rivaroxaban did not connect to the network of evidence and was not included. Across this study set, 18 interventions were evaluated (apixaban, aspirin, dabigatran, dalteparin, darexaban, desirudin, edoxaban, enoxaparin, enoxaparin+GCS, enoxaparin+IPC, fondaparinux, heparin, IPC, semuloparin, tinzaparin, VFP, warfarin, and placebo). Of the 153 possible pairwise comparisons, 30 are covered by direct study comparisons. Enoxaparin was the most common comparator, being directly compared with 14 other interventions; most frequently with heparin (7 RCTs) and placebo (7 RCTs). Dalteparin was directly compared with heparin, warfarin, and placebo only; warfarin was also directly compared with aspirin and IPC; aspirin was also directly compared with placebo.

Overall, the combination of enoxaparin plus IPC had the highest probability of being among the top three interventions to prevent DVT after THR (96%), followed by apixaban (68%). The interventions likely to be among the bottom three interventions were placebo (>99%), warfarin (77%), and tinzaparin (50%) However, omitting interventions that are directly linked to two or fewer other interventions with two or fewer RCTs each (most interventions), dalteparin is most effective to prevent total DVTs, followed by enoxaparin, (unfractionated) heparin, and, finally, warfarin.

Major Bleeding: Comparison of Classes

There were 30 RCTs that evaluated interventions in at least two classes and reported major bleeding after THR. Across this study set, 9 classes were evaluated (antiplatelet drugs, DTI, FEI, FXaI, LMWH, mechanical, UFH, VKA, placebo). Of the 36 possible pairwise comparisons, 10 are covered by direct study comparisons. LMWH was the most common comparator, being directly compared with six other intervention classes; most frequently with FXaI (9 RCTs), UFH (6 RCTs) and placebo (5 RCTs). Antiplatelet drugs were directly compared with placebo only; FEI was directly compared with FXaI only.

Overall, the mechanical interventions had the highest probability of being among the top three intervention classes (>99%) to avoid major bleeding with thromboprophylaxis after THR,

followed by VKA (86%) and placebo (57%). The interventions likely to be among the bottom three interventions were FEI (>99%), UFH (88%), and antiplatelet drugs (67%) However, omitting interventions that are directly linked to two or fewer other interventions with two or fewer RCTs each (all classes except LMWH and FXaI—and placebo), LMWH resulted in fewer major bleeding events than FXaI, and placebo was least likely to cause major bleeding.

Major Bleeding: Comparison of Specific Interventions

In the analysis by drug (or mechanical device), there were 32 RCTs that evaluated at least two interventions and reported major bleeding after THR. However, one RCT of TB402 versus rivaroxaban did not connect to the network of evidence and was not included. Across this study set, 15 interventions were evaluated (apixaban, aspirin, dabigatran, dalteparin, darexaban, desirudin, edoxaban, enoxaparin, fondaparinux, heparin, IPC, semuloparin, tinzaparin, warfarin, and placebo). Of the 105 possible pairwise comparisons, 20 are covered by direct study comparisons. Enoxaparin was the most common comparator, being directly compared with 12 other interventions; most frequently with heparin (5 RCTs) and placebo (5 RCTs). Dalteparin was directly compared with heparin, warfarin, and edoxaban only; aspirin was directly compared with placebo only.

Overall, IPC had the highest probability of being among the top three interventions (>99%) to avoid major bleeding with thromboprophylaxis after THR, followed by semuloparin (61%). The interventions likely to be among the bottom three interventions were heparin (84%) and aspirin (66%). However, except for LMWH (and placebo) no intervention was directly compared to more than two other interventions by at least two RCTs each.

Key Question 6: Comparison of Different Start Times

Only two RCTs compared LMWH started at different times relative to THR surgery. There was insufficient evidence to yield conclusions.

Table EP1. Evidence profile for total hip replacement surgery

Key Question	Intervention(s)	Outcome*	SoE Grade	Design: No. Studies (N)	Study Limitations	Consistency	Precision	Reporting Bias†	Other Issues	Finding‡ — Favors: Summary OR (95% CI) or Range of Estimates
1 (Class vs. class, direct comparisons)	LMWH vs. DTI	DVT, total (see KQ 5)	Moderate	RCT: 3 (4600)	None	Consistent	Imprecise	None	None	Favors DTI: range 1.14-1.52
		DVT, proximal	High	RCT: 3 (4600)	None	Consistent	Precise	None	None	Favors DTI: range 1.35-1.89
		Bleeding, major (see KQ 5)	High	RCT: 4 (6900)	None	Consistent	Precise	None	None	Either: 0.79 (0.55, 1.14)
		Mortality, 30 day or in-hospital	Insufficient	RCT: 3 (4600)	None	Consistent	Highly imprecise	None	None	Unclear: range 0.14-3.03
		Other outcomes	Insufficient	RCT:≤2 per comparison				None	Sparse	Unclear
		All (benefits vs. harms)		*RCT: 4 (6900)*						*Favors DTI (lower risk VTE, similar risk bleeding)*
	LMWH vs. FXaI	VTE, total	Low	RCT: 7 (6389)	High RoB: 2 RCTs	Inconsistent	Precise	<80%§	None	Favors FXaI: 1.82 (1.23, 2.71)
		VTE, symptomatic	Low	RCT: 6 (5569)	High RoB: 1 RCT	Consistent	Precise	<80%§	None	Favors LMWH: 0.52 (0.31, 0.87)
		PE, total	Low	RCT: 4 (10080)** NRCS: 1 (1056)	RCT: None NRCS: High RoB	Inconsistent	Imprecise	<80%	None	Unclear: 0.33-1.67
		PE, fatal	Insufficient	RCT: 8 (11564)**	High RoB: 1 RCT			<80%	Rare events	Unclear
		PE, symptomatic	Insufficient	RCT: 5 (1468)**	High RoB: 2 RCTs			<80%	Rare events	Unclear
		DVT, total (see KQ 5)	Moderate	RCT: 9 (8645) NRCS: 1 (1056)	High RoB: 2 RCTs, NRCS	RCT: Inconsistent	RCT: Precise	None	None	RCT: Favors FXaI: 1.97 (1.42, 2.74) NRCS: Either
		DVT, symptomatic	Low	RCT: 8 (11253)	High RoB: 2 RCTs	Inconsistent	Imprecise	<80%	None	Unclear: 0.82 (0.34, 1.97)
		DVT, proximal	Moderate	RCT: 10 (9622)	High RoB: 2 RCTs	Inconsistent	Precise	None	None	Favors FXaI: 2.40 (1.23, 4.69)
		Bleeding, major (see KQ 5)	High	RCT: 9 (11756)	High RoB: 2 RCTs	Consistent	Precise	None	None	Favors LMWH: 0.72 (0.52, 0.99)
		Bleeding, fatal	Insufficient	RCT: 3 (8900)**	None	No events	Highly imprecise	--	Rare events	Unclear

Key Question	Intervention(s)	Outcome*	SoE Grade	Design: No. Studies (N)	Study Limitations	Consistency	Precision	Reporting Bias†	Other Issues	Finding‡ — Favors: Summary OR (95% CI) or Range of Estimates
		Bleeding → Reoperation	Insufficient	RCT: 3 (8900)	None	Consistent	Highly imprecise	--	None	Unclear
		Bleeding, joint	Low	RCT: 3 (8900)	None	Consistent	Imprecise	--	None	Unclear: range 0.50-0.89
		Mortality, 30 day	Insufficient	RCT: 3 (4807)**	None	Inconsistent	Highly imprecise	--	Rare events	Unclear
		Serious adverse events	Moderate	RCT: 5 (6727)	High RoB: 2 RCTs	Consistent	Precise	<80%	None	Either: 0.95 (0.78, 1.17)
		All (benefits vs. harms)		*RCT: 11 (12472)*						*Favors LMWH (unclear VTE effect, lower risk bleeding)*
	LMWH vs. Mechanical	DVT, total	Insufficient	RCT: 3 (732)	None	Consistent	Highly imprecise	None	None	Unclear
		DVT, proximal	Insufficient	RCT: 3 (732)	None	Consistent	Highly imprecise	None	None	Unclear
		Other outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear
		All (benefits vs. harms)		*RCT: 3 (732)*						*Unclear*
	LMWH vs. UFH	PE, total	High	RCT: 8 (1878)	None	Consistent	Precise	None	None	Favors LMWH: 0.26 (0.13, 0.54)
		PE, fatal	Insufficient	RCT: 7 (1711)**	None	No events	Highly imprecise	<80%	Rare events	Unclear
		DVT, total (see KQ 5)	High	RCT: 10 (2219)	None	Consistent	Precise	None	None	Either: 0.84 (0.60, 1.18)
		DVT, symptomatic	Insufficient	RCT: 4 (488)	None	Consistent	Highly imprecise	<80%	None	Unclear: 0.84 (0.32, 2.22)
		DVT, proximal	Moderate	RCT: 6 (1506)	None	Consistent	Precise	<80%	None	Favors LMWH: 0.59 (0.38, 0.93)
		Bleeding, major (see KQ 5)	Moderate	RCT: 6 (1960)	None	Consistent	Precise	<80%	None	Favors LMWH: 0.46 (0.23, 0.92)
		Bleeding, fatal	Insufficient	RCT: 6 (1308)**	None	No events	Highly imprecise	--	Rare events	Unclear
		Mortality, 30-day or in-hospital	Insufficient	RCT: 6 (1640)**	None	Consistent	Highly imprecise	--	Rare events	Unclear
		Heparin-induced thrombocytopenia	Insufficient	RCT: 3 (1163)**	None	Consistent	Highly imprecise	--	Rare events	Unclear

Key Question	Intervention(s)	Outcome*	SoE Grade	Design: No. Studies (N)	Study Limitations	Consistency	Precision	Reporting Bias†	Other Issues	Finding‡ — Favors: Summary OR (95% CI) or Range of Estimates
		All (benefits vs. harms)		*RCT: 10 (2387)*						*Favors LMWH (lower risk VTE and bleeding)*
	LMWH vs. VKA	PE, total	Insufficient	RCT: 3 (4537)**	None	Consistent	Highly imprecise	None	Rare events	Unclear
		PE fatal	Insufficient	RCT: 3 (4537)**	None	Consistent	Highly imprecise	None	Rare events	Unclear
		DVT, total	High	RCT: 3 (4537)	None	Consistent	Precise	None	None	Favors LMWH: range 0.48-0.87
		DVT, proximal	Low	RCT: 3 (4537)	None	Inconsistent	Imprecise	None	None	Unclear: range 0.27-1.27
		Bleeding, major (see KQ 5)	High	RCT: 4 (5332)	None	Consistent	Precise	None	None	Favors VKA: 1.68 (1.11, 2.53)
		Other outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear
		All (benefits vs. harms)		*RCT: 4 (5332)*						*Tradeoff (LMWH lower risk VTE, VKA lower risk bleeding)*
	Mechanical vs. UFH	DVT, total	Low	RCT: 3 (434)	None	Inconsistent	Imprecise	None	None	Unclear: range 0.18-1.00
		DVT, proximal	High	RCT: 3 (434)	None	Consistent	Precise	None	None	Favors VKA: range 2.39-4.69
		Other outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear
		All (benefits vs. harms)		*RCT: 3 (434)*						*Unclear (UFH lower risk VTE, insufficient for bleeding)*
2 (Intervention vs. intervention, direct comparisons)	All comparisons	All outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear
3 (Different doses)	FXaI low vs. high dose	VTE, total	Low	RCT: 5 (1524)	High RoB: 2 RCTs	Inconsistent	Precise	None	None	Favors high dose: 1.48 (0.92, 2.38)
		Other outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear

Key Question	Intervention(s)	Outcome*	SoE Grade	Design: No. Studies (N)	Study Limitations	Consistency	Precision	Reporting Bias†	Other Issues	Finding‡ — Favors: Summary OR (95% CI) or Range of Estimates
	LMWH low vs. high dose	DVT, total (see KQ 5)	Moderate	RCT: 5 (1441)	High RoB: 1 RCT	Inconsistent	Precise	None	None	Favors low dose: 0.46 (0.28, 0.75)
		DVT, proximal	Low	RCT: 4 (1047)	High RoB: 1 RCT	Consistent	Imprecise	None	None	Unclear: 0.72 (0.38, 1.36)
		Bleeding, major (see KQ 5)	Insufficient	RCT: 4 (1498)	High RoB: 1 RCT	Inconsistent	Highly imprecise	None	None	Unclear: 1.39 (0.47, 4.14)
		Other outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear
		All (benefits vs. harms)		*RCT: 5 (1441)*						*Unclear (UFH lower risk VTE, insufficient for bleeding)*
	Other comparisons	All outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear
3 (Different durations)	LMWH short vs. long duration	PE, total	Moderate	RCT: 5 (1128)	None	Consistent	Imprecise	None	None	Favors long duration: 2.73 (0.97, 7.64)
		PE, fatal	Insufficient	RCT: 4 (1087)**	None	Consistent	Highly imprecise	<80%	Rare events	Unclear
		DVT, total	High	RCT: 6 (1463)	None	Consistent	Precise	None	None	Favors long duration: 2.87 (2.08, 3.96)
		DVT, symptomatic	Insufficient	RCT: 3 (1258)	None	Inconsistent	Highly imprecise	<80%	None	Unclear: range 0.53-4.20
		DVT, proximal	Moderate	RCT: 5 (1300)	None	Consistent	Precise	<80%	None	Favors long duration: 2.94 (1.62, 5.35)
		Bleeding, major	Insufficient	RCT: 3 (895)**	None	Consistent	Highly imprecise	<80%	None	Unclear
		Bleeding, fatal	Insufficient	RCT: 4 (1135)**	None	No events	Highly imprecise	--	None	Unclear
		Mortality, 30 day	Insufficient	RCT: 3 (873)**	None	Consistent	Highly imprecise	--	None	Unclear
		Other outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear

Key Question	Intervention(s)	Outcome*	SoE Grade	Design: No. Studies (N)	Study Limitations	Consistency	Precision	Reporting Bias†	Other Issues	Finding‡ — Favors: Summary OR (95% CI) or Range of Estimates
		All (benefits vs. harms)		*RCT: 6 (1463)*						*Long duration (Long duration lower risk VTE, bleeding events rare)*
	Other comparisons	All outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear
4 (Single vs. combination classes)	All comparisons	All outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear
5 (Ranking of class vs. class, per NMA)	All classes‖	DVT, total	Moderate	RCT: 50	None	Consistent	Precise††	None	Few direct comparisons	FXaI and DTI most effective. ‡‡ Mechanical devices and LMWH middle effectiveness. ‡‡ UFH and VKA least effective. ‡‡
		Bleeding, major	Low	RCT: 30	None	Consistent	Precise††	<80%	Very few direct comparisons	Favors LMWH over FXaI**
5 (Ranking of intervention vs. intervention, per NMA)	All interventions#	DVT, total	Moderate	RCT: 51	None	Consistent	Precise††	None	Few direct comparisons	Favors dalteparin > enoxaparin > UFH > warfarin**
		Bleeding, major	Insufficient	RCT: 32	None	Consistent	Imprecise	<80%	Sparse direct comparisons	Unclear
6 (Different start times)	All comparisons	All outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear

* Evaluated outcomes included total venothromboembolism (VTE), symptomatic VTE, total pulmonary embolism (PE), fatal PE, symptomatic PE, total deep vein thrombosis (DVT), symptomatic DVT, proximal DVT, postthrombotic syndrome, pulmonary hypertension, major bleeding (total), surgical site or wound bleeding, other major bleeding (specific), surgical site or wound infection, surgical site or wound complications (other than bleeding or infection), heparin-induced thrombocytopenia, mechanical device complications, inferior vena cava filter complications, and other clinically significant adverse events.

† None = none detected; <80% = <80% of studies of drug comparison reported given outcome, unless only one missing study (data on all VTE and major bleeding outcomes should have been available in almost all trials; therefore, outcomes were excluded selectively suggesting high risk of bias of reporting bias). Other issues as noted. -- = Evaluation omitted for specific adverse events and non-VTE outcomes (as these are not part of standard reporting).

‡ "Unclear" can also be interpreted as no evidence of a difference (in contrast to evidence of no difference).

§ Different trials reported either total VTE or symptomatic VTE resulting in conflicting findings between the two outcomes (FXaI results in fewer total VTE, but LMWH results in fewer symptomatic VTE).
|| Antiplatelet drugs, direct thrombin inhibitors, factor VIII inhibitors, factor Xa inhibitors, low molecular weight heparin, mechanical device, unfractionated heparin, vitamin K antagonist, and combination low molecular weight heparin and mechanical device.
Apixaban, aspirin, dabigatran, dalteparin, darexaban, desirudin, edoxaban, enoxaparin, fondaparinux, heparin (unfractionated), intermittent pneumatic compression device, semuloparin, tinzaparin, venous foot pump, warfarin, combination enoxaparin and graduated compression stocking, and combination enoxaparin and intermittent pneumatic compression.
**Fewer than 3 RCTs per comparison for individual outcome were analyzable, because other RCTs had no events.
†† Among the described interventions. Too few RCTs evaluated other interventions resulted in insufficient evidence.
‡‡ Among classes (or interventions) compared to at least two other classes (or interventions) by at least 2 trials.

Other abbreviations: LMWH = low molecular weight heparin, DTI = direct thrombin inhibitor, FXaI = factor Xa inhibitor, UFH = unfractionated heparin, VKA = vitamin K antagonist, UFH = unfractionated heparin, OR = odds ratio, RCT = randomized controlled trial, NMA = network meta-analysis.

Total Knee Replacement

Across Key Questions, 54 eligible studies evaluated thromboprophylaxis interventions in patients who underwent TKR. The largest number compared different classes of interventions (relevant to Key Questions 1 and 5). The most commonly evaluated intervention class was LMWH, mostly in comparison with DTI, FXaI, and VKA. Other interventions were relatively infrequently evaluated in comparative effectiveness trials (i.e., comparisons of active, nonplacebo interventions). The most commonly evaluated outcomes were total DVT and major bleeding. Strength of evidence is summarized in **Table EP2.**

Key Question 1: Comparison of Intervention Classes

Note that for all three surgeries, network meta-analyses comparing classes in regard to total DVT and major bleeds are presented under Key Question 5. The results of comparisons with what was deemed to have sufficient evidence are summarized here; other comparisons are noted, but were deemed to have insufficient evidence.

Key Points

- 28 RCTs and 6 NRCSs compared classes of interventions in patients undergoing TKR.
- Pairwise comparisons between classes had sufficient data for meta-analyses for only two pairs of classes.
    - LMWH vs. FXaI: Overall, favors FXaI, with lower risk of total DVT (low SoE), but similar risks for other types of VTE (low to moderate SoE) and similar risks of major bleeding and serious adverse events (low SoE).
    - LMWH vs. VKA: Overall, an apparent tradeoff in risks with lower risk of total DVT with LMWH (high SoE), similar risks of proximal DVT (low SoE), and lower risk of major bleeding with VKA (low SoE).
    - For all other class comparisons and outcomes there was insufficient evidence.
    - Although studies reasonably should have had data for all VTE-related outcomes and for major bleeding and other serious adverse events, most outcomes were not reported by many studies, resulting in a high risk of reporting bias across the evidence base.
- A within-study subgroup analysis did not find a substantial difference in relative effect of antiplatelet drug vs. mechanical device between unilateral or bilateral TKR surgery.
- Industry-funded studies had similar finding as other studies. Asian studies had similar findings as non-Asian studies.

Summary Results

Pairwise comparisons between classes had sufficient data for only two pairs of classes. For the comparison of **LMWH versus FXaI**, across 10 RCTs, meta-analysis significantly favored LMWH to prevent total DVT (7 RCTs), but there was no statistically significant difference for total VTE (4 RCTs), symptomatic DVT (8 RCTs), proximal DVT (5 RCTs), major bleeding (7 RCTs), or serious adverse events (4 RCTs).

Among 4 RCTs that compared **LMWH versus VKA**, 3 RCTs favored LMWH to prevent total DVT, 4 RCTs in aggregate did not favor either intervention calss to prevent proximal DVT, and 4 RCTs found lower risk of major bleeding with VKA.

Other intervention classes compared by fewer studies (with insufficient evidence) included antiplatelet drugs versus FXaI, antiplatelet drugs versus mechanical devices, antiplatelet drugs versus VKA, DTI versus FXaI, LMWH versus antiplatelet drugs, LMWH versus DTI, LMWH versus FXIi, LMWH versus mechanical devices, and LMWH versus UFH.

Subgroup Analysis

One RCT compared subgroups of patients who received unilateral or bilateral TKR surgery in a comparison of antiplatelet drug versus mechanical device. They found that in the unilateral group (n=72) the percent of patients with a DVT was lower for those receiving mechanical prophylaxis through a compression boot (22%) compared to those receiving aspirin (47%, P<0.03). In the bilateral group (n=47), DVT incidence was also lower in patients who used compression boots (48%) compared with those who received aspirin (68%), but this difference was not significant (P<0.20). Whether the treatment effect differed between unilateral and bilateral subgroups was not analyzed.

Studies were generally homogeneous in terms of patient eligibility criteria, such that most across-study comparisons of subgroup factors are limited.

Among TKR RCTs, differences between studies based on industry funding was analyzable for only the comparison of LMWH versus FXaI. For total DVT, by random effects model metaregresion no significant difference (P=0.21) was found between the six industry-funded studies (summary OR 2.04, 95% CI 1.68 to 2.49) and the single study without industry support (OR 4.71, 95% CI 1.31 to 16.9).

For the comparison of Asian versus non-Asian RCTs, only the comparison of LMWH versus FXaI was analyzable. For total DVT, no significant difference (P=0.97) was found between the four Asian studies (summary OR 2.15, 95% CI 1.35 to 3.41) and three non-Asian studies (summary OR 2.12, 95% CI 1.59 to 2.82) by random effects model metaregresion. However, the total DVT rate was lower in the Asian RCTs (9.6%) than the non-Asian studies (16.0%, P<0.01). Similarly, for major bleeding, no significant difference (P=0.34) was found between the two Asian studies (summary OR 0.27, 95% CI 0.03 to 2.32) and the five non-Asian studies (OR 0.89, 95% CI 0.29 to 2.72). Major bleeding rates were similar between Asian studies (0.7%) and non-Asian studies (0.9%, P=0.57).

Key Question 2: Comparison of Within-Class Interventions

Note that for all three surgeries, network meta-analyses comparing individual interventions in regard to total DVT and major bleeds are presented under Key Question 5.

Relatively few RCTs of venoprophylaxis compared specific interventions within any given class (2 for TKR). No comparison was evaluated by more than two studies. In patients undergoing TKR, one or two RCTs each evaluated enoxaparin versus semuloparin (LMWHs), enoxaparin versus tinzaparin (LMWHs), and graduated compression stockings versus intermittent pressure devices (mechanical devices). Evidence was insufficient to evaluate within-class intervention comparisons.

Key Question 3: Comparison of Dosages and Treatment Durations

Key Points

- 16 RCTs and 1 NRCS compared different intervention doses or durations in patients undergoing TKR.

- DTI low vs. high dose: There is low SoE that the risk of bleeding is similar with low or high dose DTI, but insufficient evidence for VTE outcomes.
- FXaI low vs. high dose: There is moderate SoE that high dose FXaI yields a lower risk of total VTE and symptomatic DVT, but that both result in similar risk proximal DVT, and insufficient evidence for adverse events.

More than 300 specific comparisons of different drug doses or device regimens have been reported; the large majority of specific comparisons were made by a single study only. Comparisons with sufficient evidence are summarized here. These all pertain to class-level analyses; specific intervention comparisons were not evaluated with sufficient frequency to allow a conclusion of sufficient evidence.

For only two pairwise comparisons of dose or treatment duration was there sufficient data. Four RCTs found no significant difference in major bleeding for the comparison of low versus high dose DTI.. Data for other outcomes, including VTE, were insufficient.

Four RCTs that examined relative effectiveness of low versus high doses of FXaI found a statistically significantly lower risk of total VTE and symptomatic DVT with high dose FXaI. The 4 RCTs failed to find a significant difference between low and high dose FXaI to prevent proximal DVTs. Data for other outcomes, including major bleeding, were insufficient.

Key Question 4: Comparison of Single Versus Combination Classes

Key Points

- 6 RCTs and 2 NRCSs compared single versus combined classes of intervention in patients undergoing THR, 5 RCTs and 3 NRCSs in patients undergoing TKR, and 1 NRCS in patients undergoing HFx surgery.
- Overall, there was insufficient evidence regarding the differences between combined or single classes of interventions to prevent VTE or avoid adverse events.

Note that for all three surgeries, network meta-analyses comparing individual interventions (including combination interventions) in regard to total DVT and major bleeds are presented under Key Question 5. However, in pairwise comparisons, relatively few studies directly compared combination versus single interventions. Most specific comparisons were made by one study only.

For TKR, RCTs provided insufficient evidence for comparisons of antiplatelet drug versus combination antiplatelet drug and mechanical device; LMWH alone versus combinations of LMWH and FEI or mechanical device, and UFH alone versus combination UFH and LMWH.

Key Question 5: Network Meta-Analyses

Key Points

- Conclusions from all NMAs are limited due to the sparseness of direct comparisons between most interventions within each network.
- For patients undergoing TKR, comparisons between specific pairs of classes or of intereventions were too sparse to yield sufficient conclusions regarding risks of total DVT or major bleeding.

- For TKR, 28 RCTs compared classes of interventions for total DVT and 21 compared classes of interventions for major bleeding; 4 RCTs compared specific interventions for total DVT and 22 for major bleeding.

DVT: Comparison of Classes

There were 28 RCTs that evaluated interventions in at least two classes and reported total DVT after TKR. Across this study set, 11 classes were evaluated (antiplatelet drugs, antiplatelet drugs + mechanical, DTI, FXaI, FXIi, LMWH, LMWH+mechanical, Mechanical, UFH, VKA, placebo). Of the 55 possible pairwise comparisons, 18 are covered by direct study comparisons. LMWH was the most common comparator, being directly compared with nine other intervention classes; most frequently with FXaI (7 RCTs). The combination of antiplatelet drugs plus mechanical was directly compared with antiplatelet drugs only.

Overall, FXaI had the highest probability of being among the top three intervention classes (89%) to prevent DVT after TKR, followed closely by the combination of antiplatelet drugs plus mechanical (87%), then DTI (57%). The interventions likely to be among the bottom three interventions were placebo (>99%), antiplatelet drugs (83%), and VKA (82%). However, except for enoxaparin (and placebo) no intervention was directly compared to more than two other interventions by at least two RCTs each.

DVT: Comparison of Specific Interventions

In the analysis by drug (or mechanical device), there were 30 RCTs that evaluated at least two interventions and reported total DVT after TKR. Across this study set, 21 interventions were evaluated (apixaban, aspirin, aspirin+VFP, dabigatran, darexaban, edoxaban, enoxaparin, enoxaparin+GCS, enoxaparin+IPC, enoxaparin+VFP, flexion, fondaparinux, FXIASO, heparin, IPC, rivaroxaban, semuloparin, tinzaparin, VFP, warfarin, placebo). Of the 210 possible pairwise comparisons, 32 are covered by direct study comparisons. Enoxaparin was the most common comparator, being directly compared with 16 other interventions. Flexion was directly compared with placebo only; enoxaparin+GCS was directly compared with enoxaparin+IPC only; IPC and aspirin+VFP were directly compared with aspirin only.

Overall, rivaroxaban had the highest probability of being among the top three interventions to prevent DVT after TKR, followed by the combination of enoxaparin plus VFP (66%) and the combination of aspirin plus VFP (59%). The interventions likely to be among the bottom three interventions were the combination of enoxaparin plus GCS (>99%), placebo (77%), and flexion device (67%). However, except for enoxaparin (and placebo) no intervention was directly compared to more than two other interventions by at least two RCTs each.

Major Bleeding: Comparison of Classes

There were 22 RCTs that evaluated interventions in at least two classes and reported major bleeding after TKR. However, one RCT of antiplatelet drugs versus the combination of antiplatelet drugs plus mechanical did not connect to the network of evidence and was not included. Across this study set, 7 classes were evaluated (DTI, FXaI, FXIi, LMWH, UFH, VKA, placebo). Of the 21 possible pairwise comparisons, 9 are covered by direct study comparisons. LMWH was the most common comparator, being directly compared with each of the six other intervention classes; most frequently with FXaI (7 RCTs), DTI (5 RCTs), and VKA (4 RCTs).

Overall, VKA had the highest probability of being among the top three intervention classes

(97%) to avoid major bleeding with thromboprophylaxis after TKR. Notably, though the mechanical devices RCTs did not provide major bleeding data. The interventions likely to be among the bottom three interventions were FXaI (75%) and FXIi (67%). However, except for LMWH (and placebo) no intervention was directly compared to more than two other interventions by at least two RCTs each.

Major Bleeding: Comparison of Specific Interventions

In the analysis by drug (or mechanical device), there were 23 RCTs that evaluated at least two interventions and reported major bleeding after TKR. However, one RCT of aspirin versus the combination of aspirin plus VFP did not connect to the network of evidence and was not included. Across this study set, 14 interventions were evaluated (apixaban, dabigatran, darexaban, edoxaban, enoxaparin, eribaxaban, fondaparinux, FXIASO, heparin, semuloparin, TAK422, tinzaparin, warfarin, placebo). Of the 91 possible pairwise comparisons, 21 are covered by direct study comparisons. Enoxaparin was the most common comparator, being directly compared with each of the 13 other interventions; most frequently with dabigatran (5 RCTs).

Across all comparisons, there were no statistically significant differences. Overall, FXIASO had the highest probability of being among the top three interventions (67%) to avoid major bleeding with thromboprophylaxis after TKR, followed by eribaxaban (61%). Notably, though the mechanical devices RCTs did not provide major bleeding data. The interventions likely to be among the bottom three interventions were darexaban (98%), fondaparinux (87%) and edoxaban (55%). However, except for enoxaparin no intervention was directly compared to more than two other interventions by at least two RCTs each.

Key Question 6: Comparison of Different Start Times

No eligible studies evaluated patients with TKR.

Table EP2. Evidence profile for total knee replacement surgery

Key Question	Intervention(s)	Outcome*	SoE Grade	Design: No. Studies (N)	Study Limitations	Consistency	Precision	Reporting Bias†	Other Issues	Finding‡ — Favors: Summary OR (95% CI) or Range of Estimates
1 (Class vs. class, direct comparisons)	Antiplatelet vs. FXaI	All outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear
	Antiplatelet vs. Mechanical	All outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear
	Antiplatelet vs. VKA	All outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear
	DTI vs. FXaI	All outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear
	LMWH vs. Antiplatelet	All outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear
	LMWH vs. DTI	DVT, symptomatic	Insufficient	RCT: 3 (2906)	None	Inconsistent	Highly imprecise	<80%	None	Unclear: 0.67-7.96
		Bleeding, major (see KQ 5)	Insufficient	RCT: 5 (3514)	None	Consistent	Highly Imprecise	None	None	Unclear: 0.96 (0.43, 2.16)
		Other outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear
	LMWH vs. FXaI	VTE, total	Moderate	RCT: 4 (1260)	High RoB: 1 RCT	Consistent	Precise	<80%	None	Either: 1.33 (0.89, 1.99)
		VTE, symptomatic	Insufficient	RCT: 3 (2058)	High RoB: 1 RCT	Inconsistent	Highly imprecise	<80%	None	Unclear: 0.25-2.02
		PE, total	Insufficient	RCT: 5 (4693)‡	High RoB: 2 RCTs	Conistent	Highly imprecise	<80%	Sparse	Unclear: 0.14-2.59
		PE, fatal	Insufficient	RCT: 5 (5214)‡	High RoB: 1 RCT	Inconsistent	Highly imprecise	<80%	None	Unclear: 0.20-1.00
		PE, symptomatic	Insufficient	RCT: 3 (121)‡	High RoB: 1 RCT	Consistent	Highly imprecise	<80%	None	Unclear
		DVT, total (see KQ 5)	Low	RCT: 7 (3805)	High RoB: 3 RCTs	Consistent	Precise	<80%	None	Favors FXaI: 2.09 (1.70, 2.58)
		DVT, symptomatic	Low	RCT: 8 (5715)	High RoB: 3 RCTs	Consistent	Imprecise	None	None	Either: 0.99 (0.51, 1.91)
		DVT, proximal	Low	RCT: 5 (2011)	High RoB: 1 RCT	Consistent	Imprecise	<80%	None	Either: 1.32 (0.62, 2.82)
		Bleeding, major (see KQ 5)	Low	RCT: 7 (5926)	High RoB: 2 RCTs	Inconsistent	Imprecise	<80%	None	Either: 0.74 (0.42, 1.30)

Key Question	Intervention(s)	Outcome*	SoE Grade	Design: No. Studies (N)	Study Limitations	Consistency	Precision	Reporting Bias†	Other Issues	Finding‡ — Favors: Summary OR (95% CI) or Range of Estimates
		Mortality, 30 day	Insufficient	RCT: 3 (3189)‡	High RoB: 1 RCT	Inconsistent	Highly imprecise	--	None	Unclear
		Serious adverse events	Low	RCT: 4 (1803)	High RoB: 1 RCT	Consistent	Imprecise	<80%	None	Either: 1.51 (0.80, 2.85)
		Other outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear
		All (benefits vs. harms)		*RCT: 10 (6350)*						*Favors FXaI (lower risk DVT, unclear risk bleeding)*
	LMWH vs. FXIi	All outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear
	LMWH vs. Mechanical	All outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear
	LMWH vs. UFH	All outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear
	LMWH vs. VKA	PE, total	Insufficient	RCT: 4 (1878)	None	Consistent	Highly imprecise	None	None	Unclear: 0.61 (0.15, 2.43)
		PE, fatal	Insufficient	RCT: 3 (1742)	None	No events	Highly imprecise	None	None	Unclear
		DVT, total (see KQ 5)	High	RCT: 3 (1742)	None	Consistent	Precise	None	None	Favors LMWH: 0.42-0.67
		DVT, proximal	Low	RCT: 4 (1772)	None	Inconsistent	Imprecise	None	None	Either: 0.51 (0.21, 1.28)
		Bleeding, major (see KQ 5)	Low	RCT: 4 (1960)‡	None	Consistent	Imprecise	None	None	Favors VKA: 1.16-3.13
		Bleeding, fatal	Insufficient	RCT: 3 (1742)	None	Consistent	Highly imprecise	None	Sparse	Unclear
		Other outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear

Key Question	Intervention(s)	Outcome*	SoE Grade	Design: No. Studies (N)	Study Limitations	Consistency	Precision	Reporting Bias†	Other Issues	Finding‡ — Favors: Summary OR (95% CI) or Range of Estimates
		All (benefits vs. harms)		*RCT: 4 (1960)*						*Tradeoff (LMWH lower risk DVT, VKA lower risk bleeding)*
2 (Intervention vs. intervention, direct comparisons)	All comparisons	All outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear
3 (Different doses)	DTI low vs. high dose	Bleeding, major	Low	RCT: 4 (3612)	High RoB: 1 RCT	Consistent	Imprecise	None	None	Either: 0.98 (0.50, 1.93)
		Other outcomes	Insufficient						Sparse	Unclear
	FXaI low vs. high dose	VTE, total	Moderate	RCT: 4 (775)	High RoB: 2 RCTs	Consistent	Precise	None	None	Favors high dose: 2.31 (1.59, 3.35)
		DVT, symptomatic	Moderate	RCT: 4 (802)	High RoB: 2 RCTs	Consistent	Precise	None	None	Favors high dose: 4.76 (1.18, 19.2)
		DVT, proximal	Moderate	RCT: 4 (779)	High RoB: 2 RCTs	Consistent	Precise	None	None	Either: 2.53 (0.86, 7.47)
		Bleeding, major	Insufficient	RCT: 4 (1095)	High RoB: 2 RCTs	Consistent	Highly imprecise	None	None	Either: 1.38 (0.31, 6.08)
		Other outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear
		All (benefits vs. harms)		RCT: 4 (1095)						Favors high dose (lower risk VTE, insufficient data for bleeding)
	Dabigatran 150 mg vs. 220 mg	DVT, symptomatic	Insufficient	RCT: 3 (2879)	None	Inconsistent	Highly imprecise	None	None	Unclear
		Bleeding, major	Insufficient	RCT: 3 (3365)	None	Consistent	Highly imprecise	None	None	Unclear
		Bleeding, fatal	Insufficient	RCT: 3 (3365)	None	No events	Highly imprecise	--	None	Unclear

Key Question	Intervention(s)	Outcome*	SoE Grade	Design: No. Studies (N)	Study Limitations	Consistency	Precision	Reporting Bias†	Other Issues	Finding‡ — Favors: Summary OR (95% CI) or Range of Estimates
		Bleeding → reoperation	Insufficient	RCT: 3 (3365)	None	Consistent	Highly imprecise	--	None	Unclear
		Mortality, 30 day	Insufficient	RCT: 3 (3365)	None	Consistent	Highly imprecise	--	None	Unclear
	Other comparisons	All outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear
3 (Different durations)	All comparisons	All outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear
4 (Single vs. combination classes)	All comparisons	All outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear
5 (Ranking of class vs. class, per NMA)	All classes§	DVT, total	Low	RCT: 28	None	Consistent	Precise#	None	Very few direct comparisons	Favors FXaI over LMWH**
		Bleeding, major	Low	RCT: 22	None	Consistent	Precise#	<80%	Very few direct comparisons	Favors LMWH over FXaI**
5 (Ranking of intervention vs. intervention, per NMA)	All interventions††	DVT, total	Insufficient	RCT: 30	None	Consistent	Imprecise	None	Sparse direct comparisons	Unclear
		Bleeding, major	Insufficient	RCT: 23	None	Consistent	Imprecise	<80%	Sparse direct comparisons	Unclear
6 (Different start times)	All comparisons	All outcomes	Insufficient	RCT: 0					Sparse	Unclear

* Evaluated outcomes included total venothromboembolism (VTE), symptomatic VTE, total pulmonary embolism (PE), fatal PE, symptomatic PE, total deep vein thrombosis (DVT), symptomatic DVT, proximal DVT, postthrombotic syndrome, pulmonary hypertension, major bleeding (total), surgical site or wound bleeding, other major bleeding (specific), surgical site or wound infection, surgical site or wound complications (other than bleeding or infection), heparin-induced thrombocytopenia, mechanical device complications, inferior vena cava filter complications, and other clinically significant adverse events.

† None = none detected; <80% = <80% of studies of drug comparison reported given outcome, unless only one missing study (data on all VTE and major bleeding outcomes should have been available in almost all trials; therefore, outcomes were excluded selectively suggesting high risk of bias of reporting bias). Other issues as noted. -- = Evaluation omitted for specific adverse events

‡ Fewer than 3 RCTs per comparison for individual outcome were analyzable, because other RCTs had no events.

§ Antiplatelet drugs, direct thrombin inhibitors, factor VIII inhibitors, factor Xa inhibitors, low molecular weight heparin, mechanical device, unfractionated heparin, vitamin K antagonist, and combination low molecular weight heparin and mechanical device.

Among the described interventions. Too few RCTs evaluated other interventions resulted in insufficient evidence.

** Among classes (or interventions) compared to at least two other classes (or interventions) by at least 2 trials.

†† Apixaban, aspirin, dabigatran, dalteparin, darexaban, desirudin, edoxaban, enoxaparin, fondaparinux, heparin (unfractionated), intermittent pneumatic compression device, semuloparin, tinzaparin, venous foot pump, warfarin, combination enoxaparin and graduated compression stocking, and combination enoxaparin and intermittent pneumatic compression.

Other abbreviations: LMWH = low molecular weight heparin, DTI = direct thrombin inhibitor, FXaI = factor Xa inhibitor, VKA = vitamin K antagonist, OR = odds ratio, RCT = randomized controlled trial, NMA = network meta-analysis.

Hip Fracture Surgery

Across Key Questions, 12 eligible studies evaluated thromboprophylaxis interventions in patients who underwent HFx surgery. No comparison between classes, interventions, or intervention regimens was evaluated by more than three studies, mostly by only one RCT. Strength of evidence is insufficient throughout and summarized in **Table EP3.**

Key Question 1: Comparison of Intervention Classes

Note that for all three surgeries, network meta-analyses comparing classes in regard to total DVT and major bleeds are presented under Key Question 5. The results of comparisons with what was deemed to have sufficient evidence are summarized here; other comparisons are noted, but were deemed to have insufficient evidence.

Key Points

- 6 RCTs compared classes of interventions in patients undergoing HFx surgery.
- There is moderate SoE that for LMWH vs. FXaI, LMWH results in a lower risk of total DVT. There is insufficient evidence for all other outcomes for this comparison and for all other intervention class comparisons.

Only 6 RCTs of venoprophylaxis have been conducted comparing intervention classes in patients undergoing HFx surgery. Pairwise comparisons between classes had sufficient data only for the comparison of LMWH versus FXaI (**Table C**). The 3 RCTs that compared **LMWH versus FXaI** found lower risk of total DVT with LMWH, but there was insufficient evidence regarding other outcomes. Other interventions classes compared included antiplatelet drugs versus mechanical devices, antiplatelet drugs versus VKA, and LMWH versus UFH; there was insufficient evidence regarding these comparisons.

Key Question 2: Comparison of Within-Class Interventions

Note that for all three surgeries, network meta-analyses comparing individual interventions in regard to total DVT and major bleeds are presented under Key Question 5.

Relatively few RCTs of venoprophylaxis compared specific interventions within any given class (2 for HFx surgery). No comparison was evaluated by more than two studies.

In patients with HFx surgery, one RCT each compared enoxaparin versus dalteparin (LMWHs) and enoxaparin versus semuloparin (LMWHs). Evidence was insufficient to evaluate within-class intervention comparisons.

Key Question 3: Comparison of Dosages and Treatment Durations

One RCT each compared different duration FXaI and LMWH, providing insufficient evidence.

Key Question 4: Comparison of Single Versus Combination Classes

No studies compared single class and combination class interventions after HFx surgery.

Key Question 5: Network Meta-Analyses

Key Points

- Conclusions from all NMAs are limited due to the sparseness of direct comparisons between most interventions within each network.
- For patients undergoing HFx surgery, comparisons between specific pairs of classes or of intereventions were too sparse to yield sufficient conclusions regarding risks of total DVT or major bleeding.
    - 6 RCTs compared classes of interventions for total DVT and 21 compared classes of interventions for major bleeding; 8 RCTs compared specific interventions for total DVT and 6 for major bleeding.

DVT: Comparison of Classes

There were six RCTs that evaluated interventions in at least two classes and reported total DVT after HFx surgery. However, one RCT of antiplatelet drugs versus mechanical did not connect to the network of evidence. Across this study set, four classes were evaluated (FXaI, LMWH, UFH, placebo). Of the six possible pairwise comparisons, four are covered by direct study comparisons. LMWH was directly compared with each of the three other intervention classes; FXaI was also directly compared with placebo.

Overall, FXaI and UFH were likely to be among the top two interventions whereas placebo and LMWH were likely to be among the bottom two interventions. However, data were sparse and only LMWH was directly compared to more than two other interventions by at least two RCTs each (for two comparisons).

DVT: Comparison of Specific Interventions

In the analysis by drug (or mechanical device), there were eight RCTs that evaluated at least two interventions and reported total DVT after HFx surgery. One RCT of aspirin versus VFP did not connect to the network of evidence. Across this study set, seven interventions were evaluated (dalteparin, edoxaban, enoxaparin, fondaparinux, heparin, semuloparin, placebo). Of the 21 possible pairwise comparisons, 8 are covered by direct study comparisons. Enoxaparin was the most common comparator, being directly compared with five other interventions. Heparin was directly compared with dalteparin only.

Overall, heparin (99%) and fondaparinux (98%) had the highest probabilities of being among the top three interventions to prevent DVT after HFx surgery, followed by dalteparin (78%). The other three interventions were likely to be among the bottom three interventions: placebo (98%), enoxaparin (93%), and edoxaban (82%) However, no intervention was directly compared to two other interventions by at least two RCTs.

Major Bleeding: Comparison of Classes

There were four RCTs that evaluated interventions in at least two classes and reported major bleeding after HFx surgery. Across this study set, five classes were evaluated (antiplatelet drugs, FXaI, LMWH, VKA, placebo). Of the 10 possible pairwise comparisons, 6 are covered by direct study comparisons. Placebo was the most common comparator, being directly compared with each of the five other intervention classes.

There were no statistically significant differences. Overall, antiplatelet drugs had the highest

probability of being among the top two interventions (>99%) to avoid major bleeding with thromboprophylaxis after HFx surgery, followed by VKA (51%). The interventions likely to be among the bottom two interventions were FXaI (98%) and LMWH (98%). However, except for the comparison of LMWH and FXaI, only single RCTs compared intervention classes.

Major Bleeding: Comparison of Specific Interventions

In the analysis by drug (or mechanical device), there were six RCTs that evaluated at least two interventions and reported major bleeding after HFx surgery. Across this study set, eight interventions were evaluated (aspirin, dalteparin, edoxaban, enoxaparin, fondaparinux, semuloparin, warfarin, and placebo). Of the 28 possible pairwise comparisons, 9 are covered by direct study comparisons. Enoxaparin was the most common comparator, being directly compared with five other interventions. Aspirin and warfarin were directly compared with each other and placebo only.

There were no statistically significant differences. Overall, aspirin had the highest probability of being among the top three interventions (>99%) to avoid major bleeding with thromboprophylaxis after HFx surgery, followed by placebo (96%) and warfarin (96%). The interventions likely to be among the bottom three interventions were semuloparin (87%), fondaparinux (76%), and enoxaparin (73%). However, only enoxaparin and fondaparinux were directly compared by two RCTs.

Key Question 6: Comparison of Different Start Times

No eligible studies evaluated patients with HFx surgery. There was insufficient evidence to yield conclusions.

Table EP3. Evidence profile for hip fracture surgery

Key Question	Intervention(s)	Outcome*	SoE Grade	Design: No. Studies (N)	Study Limitations	Consistency	Precision	Reporting Bias†	Other Issues	Finding‡ — Favors: Summary OR (95% CI) or Range of Estimates
1 (Class vs. class, direct comparisons)	Antiplatelet vs. Mechanical	All outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear
	Antiplatelet vs. VKA	All outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear
	LMWH vs. FXaI	DVT, total (see KQ 5)	Moderate	RCT: 3 (1816)	None	Inconsistent	Precise	None	None	Favors LMWH: 2.71-3.81†
		DVT, proximal	Insufficient	RCT: 3 (1816)	None	Consistent	Highly imprecise	None	None	Unclear
		Bleeding, major	Insufficient	RCT: 3 (1816)	None	Inconsistent	Highly imprecise	None	None	Unclear
		All (benefits vs. harms)		*RCT: 3 (1816)*						*Favors LMWH (LMWH lower risk DVT, insufficient for bleeding)*
	LMWH vs. UFH	All outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear
2 (Intervention vs. intervention, direct comparisons)	All comparisons	All outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear
3 (Different doses)	All comparisons	All outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear
3 (Different durations)	All comparisons	All outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear
4 (Single vs. combination classes)	All comparisons	All outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear
5 (Ranking of class vs. class, per NMA)	All classes‡	DVT, total	Insufficient	RCT: 5 (2003)	None	Consistent	Imprecise	None	Sparse direct comparisons	Unclear
		Major bleeding	Insufficient	RCT: 4 (2039)	None	Consistent	Imprecise	<80%	Sparse direct comparisons	Unclear

Key Question	Intervention(s)	Outcome*	SoE Grade	Design: No. Studies (N)	Study Limitations	Consistency	Precision	Reporting Bias†	Other Issues	Finding‡ — Favors: Summary OR (95% CI) or Range of Estimates
5 (Ranking of intervention vs. intervention, per NMA)	All interventions§	DVT, total	Insufficient	RCT: 8 (3122)	None	Consistent	Imprecise	None	Sparse direct comparisons	Unclear
		Major bleeding	Insufficient	RCT: 6 (3158)	None	Consistent	Imprecise	<80%	Sparse direct comparisons	Unclear
6 (Different start times)	All comparisons	All outcomes	Insufficient	RCT:≤2 per comparison					Sparse	Unclear

* Evaluated outcomes included total venothromboembolism (VTE), symptomatic VTE, total pulmonary embolism (PE), fatal PE, symptomatic PE, total deep vein thrombosis (DVT), symptomatic DVT, proximal DVT, postthrombotic syndrome, pulmonary hypertension, major bleeding (total), surgical site or wound bleeding, other major bleeding (specific), surgical site or wound infection, surgical site or wound complications (other than bleeding or infection), heparin-induced thrombocytopenia, mechanical device complications, inferior vena cava filter complications, and other clinically significant adverse events.

† None = none detected; <80% = <80% of studies of drug comparison reported given outcome, unless only one missing study (data on all VTE and major bleeding outcomes should have been available in almost all trials; therefore, outcomes were excluded selectively suggesting high risk of bias of reporting bias). Other issues as noted. -- = Evaluation omitted for specific adverse events

† A third highly imprecise trial had an odds ratio of 0.55 (95% CI 0.05, 5.58)

‡Antiplatelet drugs, direct thrombin inhibitors, factor VIII inhibitors, factor Xa inhibitors, low molecular weight heparin, mechanical device, unfractionated heparin, vitamin K antagonist, and combination low molecular weight heparin and mechanical device.

§ Apixaban, aspirin, dabigatran, dalteparin, darexaban, desirudin, edoxaban, enoxaparin, fondaparinux, heparin (unfractionated), intermittent pneumatic compression device, semuloparin, tinzaparin, venous foot pump, warfarin, combination enoxaparin and graduated compression stocking, and combination enoxaparin and intermittent pneumatic compression.

Other abbreviations: OR = odds ratio, RCT = randomized controlled trial, NMA = network meta-analysis, DVT = deep vein thrombosis.

Discussion

A large volume of evidence has been garnered comparing intervention options to prevent venous thromboembolism (VTE) in patients undergoing total hip replacement (THR), total knee replacement (TKR), and hip fracture (HFx) surgery. In total, this systematic review addressing comparative effectiveness and harms of drug and mechanical interventions included 120 randomized controlled trials (RCT) and 14 large nonrandomized comparative studies (NRCS). However, these studies pertain to three different surgeries and include nine different classes of intervention and 21 specific interventions (plus additional combination of classes/interventions). Furthermore, the studies disproportionately (78%) evaluated low molecular weight heparin (LMWH) and enoxaparin, in particular (60%). In addition, studies differed in regard to the specific VTE outcomes that were reported. Furthermore, the large majority of studies compared different intervention classes (relevant to Key Question 1), but few compared specific interventions within a class (Key Question 2); different doses, regimens, or intervention durations (Key Question 3); combinations of intervention classes (Key Question 4); or different treatment start times (Key Question 6). Therefore, many of the conclusions (answers to the Key Questions) are highly limited due to insufficient evidence.

Evidence Summary

In summary, from direct comparisons for THR the evidence

- favors direct thrombin inhibitors (DTI) vs. LMWH to lower risk of deep vein thrombosis (DVT) with a similar risk of major bleeding (moderate to high strength of evidence [SoE])
- favors LMWH vs. factor Xa inhibitors (FXaI) to lower risk of major bleeding (high SoE) but unclear evidence regarding VTE with inconsistent findings likely due to reporting bias (low to moderate SoE)
- favors LMWH vs. unfractionated heparin (UFH) with lower risk of VTE (but similar risk of total DVT) and similar risk of major bleeding (moderate to high SoE)
- found a tradeoff between LMWH and vitamin K antagonists (VKA) such that LMWH lowers risk of DVT but VKA results in fewer episodes of major bleeding (high SoE)
- favors high dose (vs. low dose) FXaI to lower risk of total VTE (low SoE) but with insufficient evidence regarding other VTE and adverse event outcomes
- favors low dose (vs. high dose) LMWH to lower risk of total DVT (moderate SoE) but with unclear or insufficient evidence for other VTE and adverse event outcomes
- favors long duration (vs. short duration) LMWH to lower risk of VTE, but insufficient evidence for adverse events

From network meta-analyses,

- FXaI is most effective to prevent total DVT, followed by DTI, mechanical devices, LMWH, VKA, and UFH (moderate SoE)
- LMWH resulted in fewer major bleeding events than FXaI, and placebo was least likely to cause major bleeding (low SoE)
- dalteparin is most effective to prevent total DVTs, followed by enoxaparin, (unfractionated) heparin, and, finally, warfarin (moderate SoE)
- comparisons between specific pairs of interventions were too sparse to yield sufficient conclusions regarding risk of major bleeding

For other pairwise comparisons of different intervention classes or different within-class doses or treatment duration, there is insufficient evidence. Similarly, there is insufficient evidence to adequately address differences between specific interventions within the same class, comparisons of single versus combination class interventions, or different start times.

Most outcomes were not reported by many studies, resulting in a high risk of reporting bias across the evidence base. A within-study subgroup analysis was inconclusive regarding differential risks of bleeding with LMWH and DTI by chronic kidney disease stage. Industry-funded studies had similar finding as other studies. Asian studies had similar findings as non-Asian studies.

Total Knee Replacement

Fewer studies of TKR (than THR) yielded fewer conclusions with sufficient SoE. In summary, from direct comparisons for TKR the evidence

- favors FXaI vs. LMWH to lower risk of total DVT (low SoE) but with similar risks between the two classes for other types of VTE (low to moderate SoE) and similar risks of major bleeding and serious adverse events (low SoE)
- found a tradeoff between LMWH and VKA such that LMWH better lowers risk of total DVT (high SoE), with similar risks of proximal DVT (low SoE), but VKA has a lower risk of major bleeding (low SoE)
- found that high dose FXaI (vs. low dose) yields a lower risk of total VTE and symptomatic DVT (moderate SoE), but both result in similar risk of proximal DVT (moderate SoE), and there is insufficient evidence for adverse events
- found similar risk of bleeding between low and high dose DTI (low SoE), but insufficient evidence regarding VTE outcomes.

For other pairwise comparisons of different intervention classes or different within-class doses or treatment duration, there is insufficient evidence. Similarly, there is insufficient evidence to adequately address differences between specific interventions within the same class, comparisons of single versus combination class interventions, or different start times. The network meta-analyses also produced insufficient evidence to form adequate conclusions.

Most outcomes were not reported by many studies, resulting in a high risk of reporting bias across the evidence base. A within-study subgroup analysis did not find a substantial difference in relative effect of antiplatelet drug vs. mechanical device between unilateral or bilateral TKR surgery. Industry-funded studies had similar finding as other studies. Asian studies had similar findings as non-Asian studies.

Hip Fracture Surgery

Only 12 eligible studies evaluated thromboprophylaxis interventions in patients who underwent HFx surgery. Most specific comparisons were addressed by only one study. There is moderate SoE that LMWH results in lower risk of total DVT than FXaI, but insufficient evidence for other outcomes. For all other comparisons and for all other Key Questions the SoE is insufficient regarding HFx surgery.

Evidence Limitations

As noted in the evidence summary, despite the large number of trials addressing venothromboprophlaxis in patients undergoing major orthopedic surgery, there is inadequate evidence to confidently compare the effectiveness and the major adverse events of the myriad treatment options. As noted, the large majority of evidence pertains to enoxaparin, limiting the ability to compare all interventions. The network meta-analyses provided greater power to compare all intervention classes and all interventions, but the sparseness of direct (within-study) comparisons for many of the interventions meant that meaningful conclusions could be derived for only a small subset of the interventions.

Further hampering evaluation of the trials, studies were not consistent in which specific outcomes were reported. Notably only total DVT was reported by more than 80 percent of the studies. Only about half of studies reported major bleeding, the principal adverse event of concern for most interventions. Most of the principal VTE outcomes were reported by 50 percent or fewer of the studies. Only one study reported all prinicipal VTE and adverse event outcomes and only two studies reported all VTE outcomes. Full reporting of VTE outcomes and adverse events by trials would have allowed greater SoE for almost all intervention classes and several specific interventions. However, studies arbitrarily or selectively reported specific outcomes. This is highlighted by the comparison of LMWH and FXaI in THR patients where by meta-analysis seven RCTs (with over 6000 patients) found a near double odds of total VTE with LMWH, but six, mostly different RCTs (with over 5000 patients) found double the odds of symptomatic VTE with FXaI. It is reasonably likely that the explanation for the conflicting findings is reporting bias.

Our analyses did not find significant evidence of bias due to industry funding. However, 54 percent of the trials were industry-supported and only 13 percent of RCTs explicitly reported no industry support, which might partially explain the selective reporting.[157, 158] The relatively small number of RCTs available for meta-analysis for any given comparison and the small percentage of studies explicitly with no industry support meant that our analyses of industry funded required us to combine RCTs with no industry support and those that did not report funding source. If many of the studies that did not report funding were in fact industry-funded, then any real funding-source bias would have been diluted by the misclassification of funding source.

The RCTs were generally consistent in regard to their eligibility criteria, mostly including all-comers without contraindications. This approach improves the applicability of the individual trials (and thus of the systematic review). Nonetheless, effect sizes in subgroups were rarely reported in these RCTs, and it greatly hampered our ability to evaluate potential explanations for heterogeneity or to hypothesize about possible subgroup differences based on patient history or surgery or anesthesia characteristics. Other than funding source, we were able only to evaluate potential differences between Asian and non-Asian studies. Overall, we found no significant difference between studies conducted in different regions (among analyzable studies), except major bleeding for the comparison of LMWH and FXaI in patients undergoing THR (summary OR in Asian RCTs 1.95, 95% CI 0.46 to 8.22; summary OR in non-Asian studies 0.68, 95% CI 0.49 to 0.94). Nevertheless, the event rates in the Asian studies were generally lower than the non-Asian studies. It suggests incomparability in the two populations besides ethnicity, which might explain the potential difference in the treatment effects. Only two RCTs reported on within-study subgroup analyses based on chronic kidney disease stage (major bleeding,

enoxaparin vs. desirudin) and by unilateral versus bilateral TKR surgery (DVT, aspirin vs. compression boots). Neither study found a significant difference in treatment effect in the different subgroups

Future Research Recommendations

Much of the evidence base is insufficient to allow confident conclusions. Much of this lack is due to a relative sparseness of evidence evaluating interventions other than LMWH, and enoxaparin in particular. A more complete evidence base for the other treatments would allow for a stronger ranking of intervention classes, and of specific interventions, in term of risk of VTE and risk of major bleeding (and other adverse events). Currently, there has been substantially more research conducted in patients undergoing THR than TKR; further studies regarding TKR may be warranted. In particular, few RCTs have been conducted in HFx surgery.

To avoid real and perceived bias (including, in particular concerns about reporting bias), ideally, a greater number of studies should be funded independently of industry. Furthermore, to minimize bias, all studies should report the full range of outcomes of interest, regardless of study results. Trial registration *in priori* and standard reporting compliant with Consolidated Standards of Reporting Trials (CONSORT) statement also help reduce potential reporing bias. For VTE prophylaxis studies, there is a fairly standard list of VTE and adverse event outcomes that are generally accepted as being of interest. This systematic review covers a complete list of outcomes that should be reported by all studies. To reduce the risk of bias in systematic reviews, all outcomes, particularly including those with no events, should be reported. This review made no assumptions about unreported event rates. Therefore, since mechanical device studies rarely reported bleeding (or other adverse event) outcomes, our pairwise and network meta-analysis review of mechanical devices had insufficient evidence about risk of bleeding. Ideally, all existing RCTs should report their full set of outcome results. This can relatively easily be done by submitting trial results to a publicly-accessible registry such as ClinicalTrials.gov.

Larger RCTs should evaluate differences in treatment and adverse event effects in relevant subgroups of patients. Ideally, these analyses should be adequately powered. Based on our discussions with a panel of clinical experts and other key informants, the following subgroup analyses are of interest: sex, race/ethnicity, age, body weight, tobacco use, chronic disease, varicocities, history of bleeding disorders or surgical bleeding, prior VTE, presurgical use of antiplatelet drugs or warfarin, or hormones, unilateral versus bilateral surgery, use of cemented fixation, tourniquet use, tranexamic acid use, and anesthesia type. A small number of trials were explicitly limited to some of these subgroups (including no presurgical use of antithrombotics and unilateral surgery), the counterfactuals (e.g., only presurgical antithrombotics or bilateral surgery) have not been studied. Since it is unlikely that RCTs will focus on these rarer and higher-risk factors, it is more important for researchers to evaluate the subgroups within their studies, when available.

Conclusions

While a large body of RCT evidence exists on comparative effectiveness and harms of venothromboprophylaxis interventions after major orthopedic surgery, none of the Key Questions are fully and adequately addressed. The largest body of evidence exists for THR, with fewer studies of TKR, and very few studies of HFx surgery. The large majority of studies evaluated LMWH (enoxaparin, in particular) with relatively few studies evaluating other intervention classes. Only a small minority of studies reported no industry support. Studies did

not regularly report on all VTE-related and adverse effect outcomes, resulting in some suggestion of reporting bias. Almost no studies reported subgroup analyses. These limitations restrict the conclusions that can be drawn from the body of evidence.

Briefly, for patients undergoing THR, there is moderate to high SoE that FXaI and DTI are more effective than LMWH and mechanical devices to prevent VTE, which are in turn more effective than UFH and VKA (all as single treatments). FXaI and UFH result in more major bleeding episodes than DTI or LMWH; LMWH results in more major bleeding than VKA.

For patients undergoing TKR, there is low to moderate SoE that FXaI is similar in effect or more effective to prevent VTE than LMWH, with similar risk of major bleeding. LMWH and VKA have similar effect to prevent VTE and LMWH and DTI have similar risks of major bleeding.

For patient undergoing HFx surgery, there is insufficient evidence regarding relative effectiveness or adverse event risk of interventions.

Regarding other Key Questions (beyond comparative effectiveness of intervention classes), there is only sufficient evidence that, after THR, dalteparin is most effective to prevent total DVTs, followed by enoxaparin, (unfractionated) heparin, and, finally, warfarin; and that lower dose, but also longer duration, LMWH is more effective to prevent total VTE (than higher dose or shorter duration LMWH), but there is no significant difference between different LMWH doses to prevent proximal DVTs or avoid major bleeding. There is also no significant difference in total VTE between different doses of FXaI. For all other interventions, comparisons, outcomes, and Key Questions there is insufficient evidence.

Future studies, particularly of interventions other than enoxaparin, are needed to address most Key Questions. These studies, and if feasible existing studies, should report all VTE-related and adverse event outcomes. Larger trials should conduct and report subgroup analyses of interest. Ideally, more future studies should be funded independently of industry to avoid real and perceived bias.

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